* Please return all attachments with search results. Thanks.

183419 Access DB# ______

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Molly Ceperley Examiner #: 59757 Date: 03/28/06

Art Unit: 1641 Phone Number 302-0813 Serial Number: 10/669,831

Mail Box and Bldg/Room Location: Rem 3A51 Results Format Preferred (circle): PAPER DISK E-MAIL

→ REM 3C70

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: See attached bibliographic data sheet

Inventors (please provide full names): ______

Earliest Priority Filing Date: 09/24/03

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

1) Please search for [illegible] "hydrazone" [illegible] with [illegible] of the following [illegible], [illegible], [illegible], bufad, [illegible], [illegible], FSA ([illegible] albumin), KLH (keyhole limpet hemocyanin), BTG ([illegible]), OVA (ovalbumin), NHS (N-hydroxysuccinimide).

2) Please search for [illegible] (Compound 6 of Figure 6) removing the "H" [illegible] ([illegible]). Compounds 8C (N hydroxysuccinimide [illegible]) [illegible] (immunogens) show examples of [illegible] compounds.

Compound [illegible]

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher:	NA Sequence (#)	STN
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic	Dr.Link
Date Completed:	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

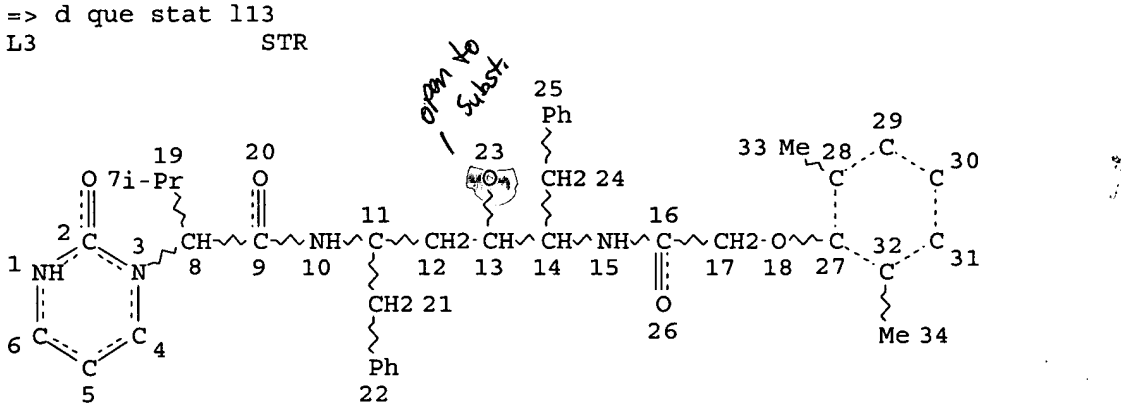
PTO-1590 (8-01)

FILE COVERS 1907 - 13 Apr 2006 VOL 144 ISS 16
FILE LAST UPDATED: 12 Apr 2006 (20060412/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que stat l13
L3 STR



NODE ATTRIBUTES:
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CONNECT IS E2 RC AT 5
CONNECT IS E2 RC AT 6
CONNECT IS E2 RC AT 29
CONNECT IS E2 RC AT 30
CONNECT IS E2 RC AT 31
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 34

STEREO ATTRIBUTES: NONE
L5 27 SEA FILE=REGISTRY SSS FUL L3
L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON 192725-17-0
L10 26 SEA FILE=REGISTRY ABB=ON PLU=ON L5 NOT L9
L11 60 SEA FILE=HCAPLUS ABB=ON PLU=ON L10
L13 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L11 AND PY<2004

← date limited

=> d l13 ibib abs hitstr 1-17

L13 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:534032 HCAPLUS
DOCUMENT NUMBER: 141:70254
TITLE: Monoclonal antibodies specific to haptens comprising protease inhibitor conjugates for immunoassay
INVENTOR(S): Sigler, Gerald F.; Hui, Raymond A.; Deras, Ina; Root, Richard Terry; Ghoshal, Mitali; Huber, Erasmus; Von Der Eltz, Herbert W.; Metz, Sigrun; Kern, Peter
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 52 pp., Cont.-in-part of U.S. Ser. No. 192,052.

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                 OR STREPTAVID? OR BSA OR BOVINE? OR KLH OR KEYHOLE? OR BTG OR
                 OVA OR OVALBUM? OR NHS OR N-HYDROXYSUCC?)
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L18          288 DUP REM L17 (218 DUPLICATES REMOVED)
                     ANSWERS '1-215' FROM FILE HCAPLUS
                     ANSWERS '216-250' FROM FILE MEDLINE
                     ANSWERS '251-256' FROM FILE EMBASE
                     ANSWERS '257-288' FROM FILE WPIX
L19           93 SEA ABB=ON  PLU=ON  L18 AND PY<2004
                 D IBIB AB L19 1 FROM EACH

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 15:51:58 ON 13 APR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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 30*  FILE CBNB
  0*  FILE CEABA-VTB
  2*  FILE CIN
  0*  FILE CIVILENG
  3*  FILE COMPENDEX
  0*  FILE COMPUSCIENCE
  0*  FILE COPPERLIT
  0*  FILE CORROSION
  0*  FILE CSNB
196   FILE DDFU
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  0*  FILE INSPEC
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 24   FILE INVESTEXT
 38   FILE IPA
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  1   FILE JICST-EPLUS
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                 SEL RN
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                 D RN
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Considered. 04/14/06 MEC

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004127689	A1	20040701	US 2003-669831	20030924
US 2003100088	A1	20030529	US 2002-192052	20020710 <--
CA 2482232	AA	20050324	CA 2004-2482232	20040920
EP 1519192	A2	20050330	EP 2004-22393	20040921
EP 1519192	A3	20050608		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2005097307	A2	20050414	JP 2004-277754	20040924
US 2005064517	A1	20050324	US 2004-982611	20041105
US 2005148596	A1	20050707	US 2004-988477	20041112

PRIORITY APPLN. INFO.: US 2001-305192P P 20010713
US 2002-192052 A2 20020710 this applicn
US 2003-669831 A 20030924

OTHER SOURCE(S): MARPAT 141:70254

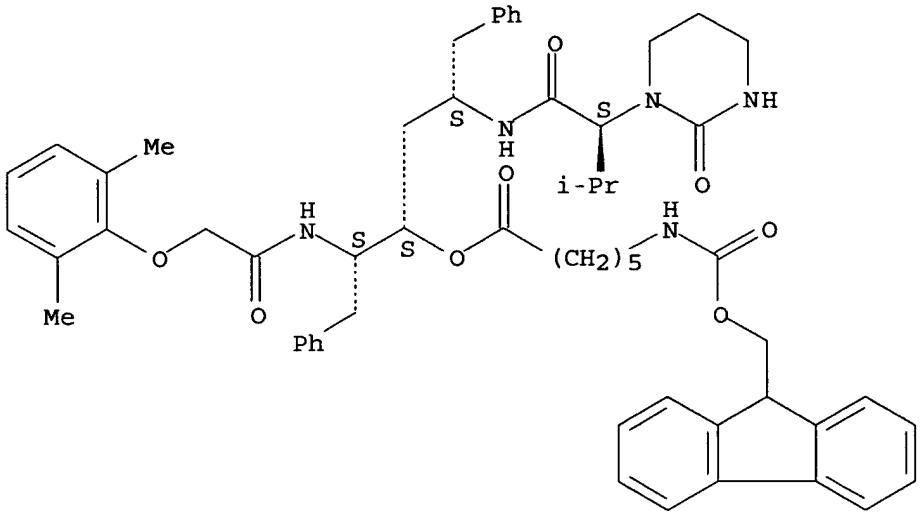
AB Activated haptens useful for generating immunogens to HIV protease inhibitors, immunogens useful for producing antibodies to HIV protease inhibitors, and antibodies and labeled conjugates useful in immunoassays for and monitoring therapeutic HIV protease inhibitors. The novel haptens feature an activated functionality at the central, non-terminal hydroxyl group common to all HIV protease inhibitors, e.g., saquinavir, nelfinavir, indinavir, amprenavir, ritonavir, lopinavir, and atazanavir.

IT **485799-46-0P 485799-47-1P 485799-48-2P**
485799-49-3P
RL: BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(monoclonal antibodies specific to haptens comprising protease inhibitor conjugates for immunoassay)

RN 485799-46-0 HCAPLUS

CN Hexanoic acid, 6-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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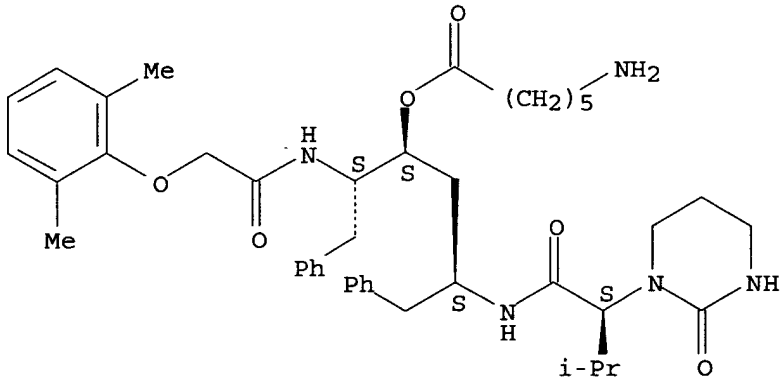
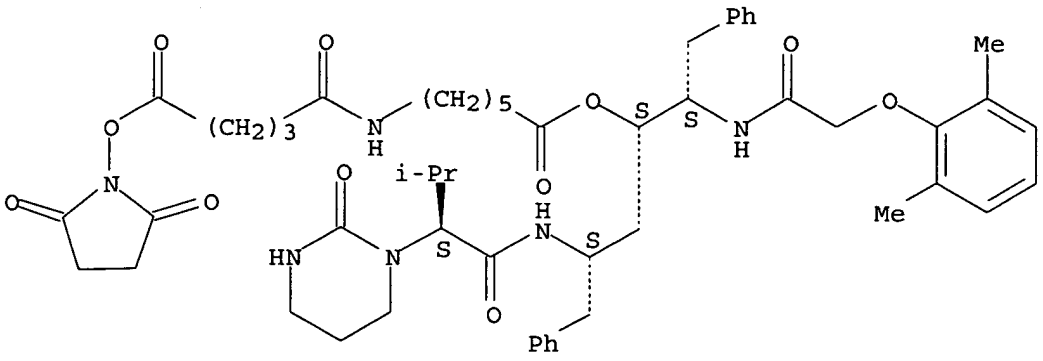
CN Hexanoic acid, 6-amino-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 485799-48-2 HCAPLUS
CN Hexanoic acid, 6-[[5-[(2,5-dioxo-1-pyrrolidinyl)oxy]-1,5-dioxopentyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

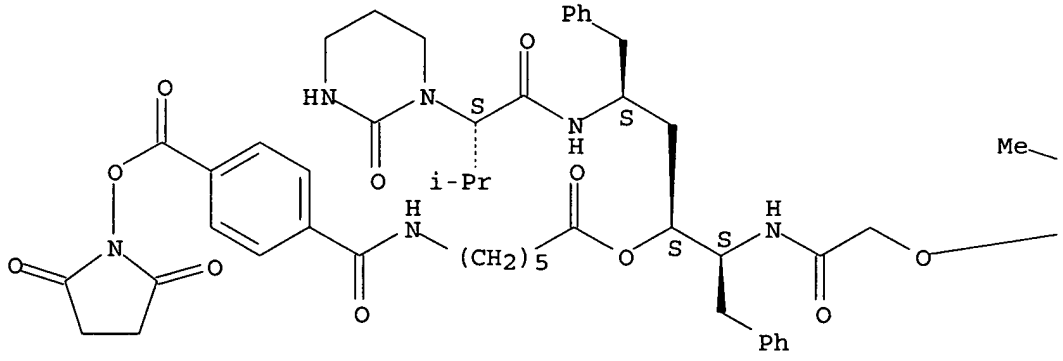
Absolute stereochemistry.



RN 485799-49-3 HCAPLUS
CN Hexanoic acid, 6-[[4-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]benzoyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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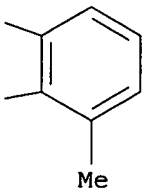


L13 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:763100 HCAPLUS
DOCUMENT NUMBER: 139:316635
TITLE: The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients
AUTHOR(S): McCance-Katz, Elinore F.; Rainey, Petrie M.; Friedland, Gerald; Jatlow, Peter
CORPORATE SOURCE: Medical College of Virginia, Virginia Commonwealth University, Richmond, USA
SOURCE: Clinical Infectious Diseases (**2003**), 37(4), 476-482
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study examines the pharmacokinetic/pharmacodynamic interactions between (1) lopinavir-ritonavir (L/R), a fixed combination of protease inhibitors used for the treatment of HIV disease, and (2) ritonavir alone at the same dosage as that in the L/R formulation, with methadone, an opiate frequently used in substance abuse pharmacotherapy for opioid (heroin)-dependent injection drug users, many of whom are infected with HIV. L/R was associated with significant redns. in the methadone area under the concentration-time curve (P <.001), maximum concentration (P <.001), and min. concentration (P <.001), as well as increased methadone oral clearance (P <.001) and increased opiate withdrawal symptoms (P =.013), whereas ritonavir use alone modestly and nonsignificantly increased methadone concns. Lopinavir is a potent inducer of methadone metabolism, and treatment with L/R requires clin. monitoring and increased methadone doses in some patients, whereas ritonavir has no significant effect on methadone metabolism

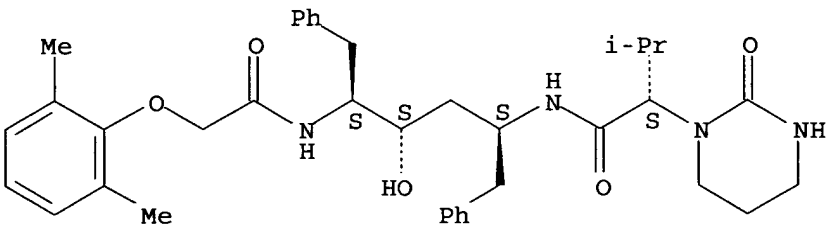
IT **369372-47-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetic and pharmacodynamic interactions and opioid withdrawal symptoms in patients receiving methadone and lopinavir-ritonavir)

RN 369372-47-4 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

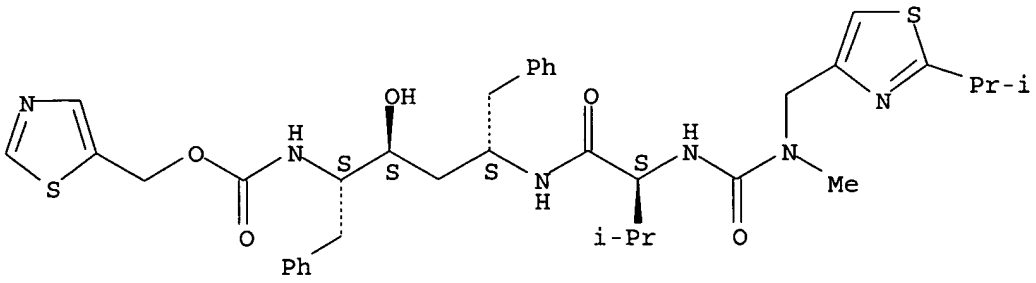
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:435315 HCAPLUS
DOCUMENT NUMBER: 139:986
TITLE: Low dosage opiate receptor antagonist in method of preventing lipodystrophy syndrome or reversing a pre-existing syndrome in HIV-infected patients being treated with antiretroviral agents
INVENTOR(S): Bihari, Bernard
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 10 pp., Cont.-in-part of U.S. Ser. No. 613,251, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2003105121	A1	20030605	US 2003-341441		20030114 <--
PRIORITY APPLN. INFO.:			US 1999-145843P	P	19990727
			US 2000-613251	B2	20000710

AB An improvement in a method of treating an HIV/AIDS infection in human patients in which the patient receives antiretroviral therapy and is consequently subjected to significant risk of developing the lipodystrophy syndrome in one or more of its characteristics is described. This risk is reduced, and pre-existing signs of such syndrome from past therapy can be substantially reversed, by the concurrent administration by a therapeutically effective mode of an essentially pure opiate receptor antagonist such as Naltrexone and Naloxone at a low level dosage.

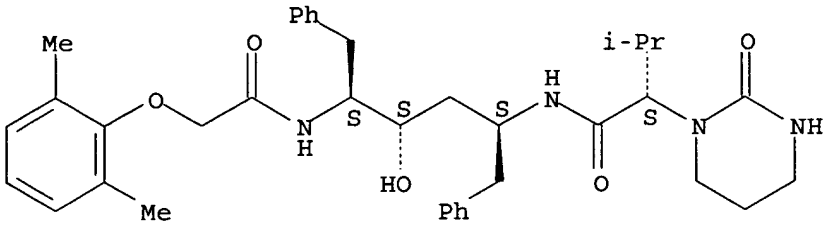
IT **369372-47-4**, Kaletra
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as antiretroviral agent; low dosage opiate receptor antagonist in prevention and treatment of lipodystrophy syndrome in HIV-infected

patients being treated with antiretroviral agents)
RN 369372-47-4 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

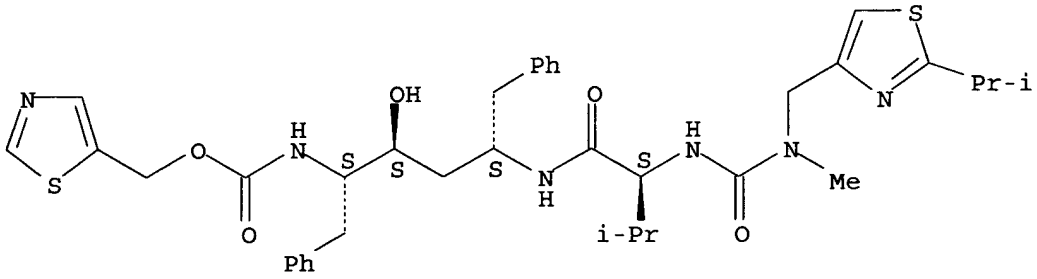
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



L13 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:431436 HCAPLUS
DOCUMENT NUMBER: 138:396188
TITLE: Elixir for the treatment of HIV infection
INVENTOR(S): Teubner, Johann
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 2 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10131036	A1	20030605	DE 2001-10131036	20010629 <--
PRIORITY APPLN. INFO.:			DE 2001-10131036	20010629

AB The invention provides an elixir for lowering the viral load of HIV. reducing side effects of antiretrovirals therapy, and increasing CD4 helper cells. The medicament of the invention includes Condurango bark, guaiac wood, dandelion roots with greens, peppermint leaves, and arnica, and 38% alc.

IT **369372-47-4**, Kaletra
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(elixir for treatment of HIV infection)

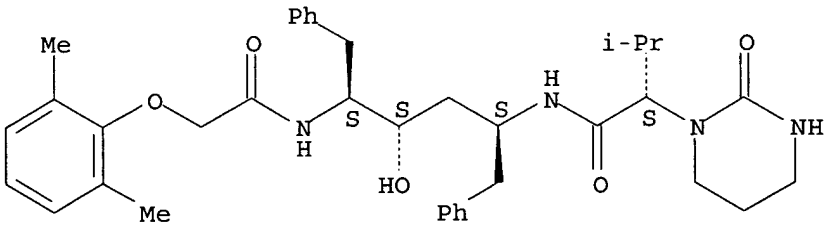
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

Absolute stereochemistry.



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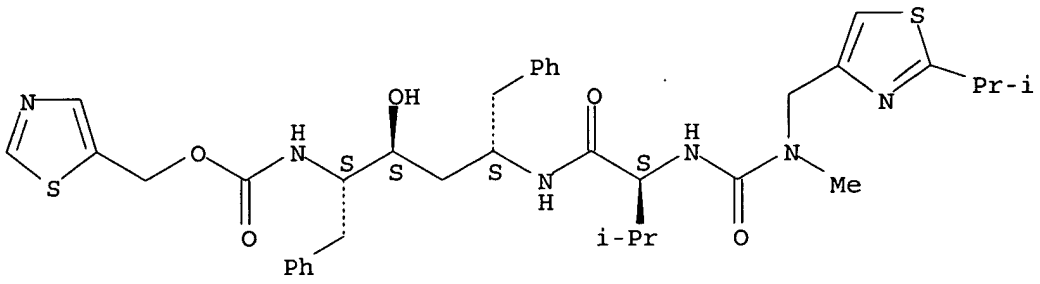
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



L13 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:359371 HCAPLUS
DOCUMENT NUMBER: 139:78307
TITLE: Lopinavir/ritonavir: A review of its use in the management of HIV infection
AUTHOR(S): Cvetkovic, Risto S.; Goa, Karen L.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (2003), 63(8), 769-802
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Lopinavir is a novel protease inhibitor (PI) developed from ritonavir. Coadministration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of lopinavir against HIV-1 protease. Coformulated lopinavir/ritonavir was developed for ease of administration and to ensure both drugs are taken together, as part of combination therapy with other antiretroviral agents. Coformulated lopinavir/ritonavir-based regimens provide adequate and durable suppression of viral load and sustained improvements in CD4+ cell counts, as demonstrated in randomized trials in antiretroviral therapy-naive and -experienced adults and children. To date, development of primary resistance to lopinavir/ritonavir has not been observed in 470 antiretroviral therapy-naive patients treated for >48 wk. The lopinavir/ritonavir-based regimen was more effective than nelfinavir in antiretroviral therapy-naive HIV-1-infected patients in a phase III trial. The coformulation is also effective as "salvage" therapy, as shown by low cross-resistance rates in patients who failed to respond to treatment with other PIs in phase II trials. Coformulated lopinavir/ritonavir was well tolerated in both antiretroviral therapy-naive and -experienced HIV-1-infected adults and children with low rates of study drug-related treatment discontinuations. The most common adverse event in adults associated with lopinavir/ritonavir was diarrhea, followed by other gastrointestinal disturbances, asthenia, headache and skin rash. The incidence of moderate-to-severe adverse events in children was low, skin rash being the most common. Changes in body fat composition occurred with equal frequency in lopinavir/ritonavir- and nelfinavir-treated naive patients, through week 60 in a phase III study. Although laboratory abnormalities occurred with similar frequency in both treatment groups, triglycerides grade 3/4 elevations were significantly more frequent with lopinavir/ritonavir. Total cholesterol and triglycerides grade 3/4 elevations appear to occur more frequently in PI-experienced than in PI-naive lopinavir/ritonavir-treated patients. A number of clin. important drug interactions have been reported with lopinavir/ritonavir necessitating dosage adjustments of lopinavir/ritonavir and/or the interacting drugs, and several other drugs are contraindicated in patients receiving the coformulation. Coformulated lopinavir/ritonavir is a novel PI that, in combination with other antiretroviral agents, suppresses plasma viral load and enhances immunol. status in therapy-naive and -experienced patients with HIV-1 infection. Lopinavir/ritonavir appears more effective than nelfinavir in "naive" patients and is also suitable for "salvage" therapy, because of its high barrier to development of resistance. Given its clin. efficacy, a tolerability profile in keeping with this class of drugs, favorable resistance profile and easy-to-adhere-to administration regimen, coformulated lopinavir/ritonavir should be regarded as a first-line option when including a PI in the management of HIV-1 infection.

IT **369372-47-4**, Kaletra

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coformulated lopinavir and ritonavir (Kaletra) for the treatment of HIV infection)

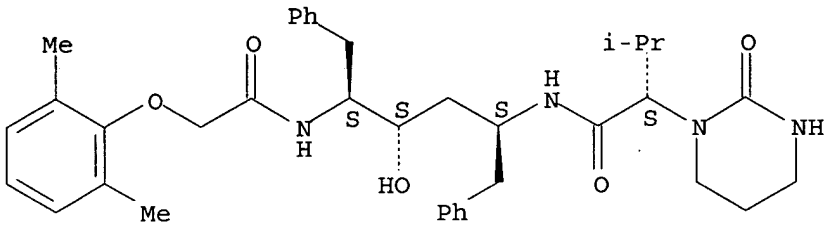
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

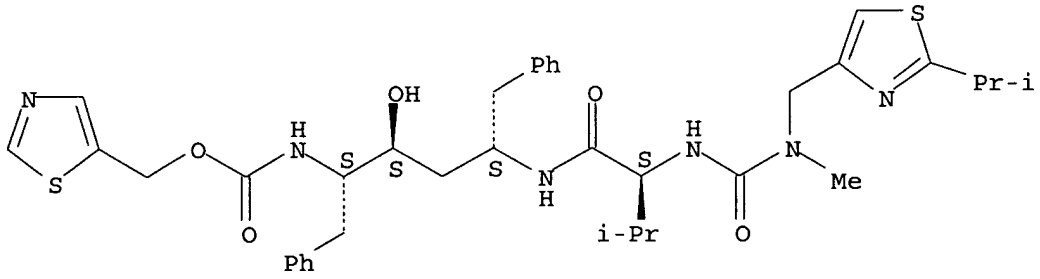
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 150 THERE ARE 150 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:343888 HCAPLUS
DOCUMENT NUMBER: 139:301355
TITLE: Decrease in LDL size in HIV-positive adults before and after lopinavir/ritonavir-containing regimen: an index

of atherogenicity?
AUTHOR(S): Badiou, S.; Merle De Boever, C.; Dupuy, A. M.; Baillat, V.; Cristol, J. P.; Reynes, J.
CORPORATE SOURCE: Department of Biochemistry, University Hospital, Montpellier, 34295, Fr.
SOURCE: Atherosclerosis (Shannon, Ireland) (**2003**), 168(1), 107-113
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypertriglyceridemia (HTG) is frequently observed during highly active antiretroviral therapy (HAART) including protease inhibitor. Apolipoprotein (apo)CIII could be involved in this HTG by inhibition of triglyceride (TG) hydrolysis, which leads to the occurrence of small dense low d. lipoprotein (sdLDL), a recognized cardiovascular risk factor. Objective was to characterize the influence of lopinavir/ritonavir-containing regimen on lipoprotein profile. 24 Antiretroviral-experienced HIV infected adults (including 14 patients in therapeutic interruption of at least 2 mo) and 14 HIV uninfected healthy controls were enrolled. Serum lipid parameters (total cholesterol (TC), HDL-C, LDL-C, TG, apoA1, apoB, apoCIII), lipoprotein composition and LDL size were determined before initiation of lopinavir/ritonavir-containing regimen, and at 1 and 3 mo thereafter. At baseline an atherogenic lipid profile was evidenced, characterized by a moderate HTG associated to a smaller mean LDL size (25.16 vs. 25.93 nm, P<0.001), an enrichment in TG of LDL (11.4 vs. 6.0%, P<0.01) and a high prevalence of sdLDL (75 vs. 7%, P<0.01) when compared to controls. After 1 mo of lopinavir/ritonavir-containing regimen, a significant reduction of LDL size (24.81 vs. 25.16 nm, P<0.05) and a significant increase in cholesterol total (5.53 vs. 4.49 mmol/l, P<0.001), in TG (4.20 vs. 2.01 mmol/l, P<0.001), in apoA1 (1.28 vs. 1.11 g/l, P<0.001), in apoB (1.08 vs. 0.94 g/l, P<0.01), in apoCIII (0.16 vs. 0.10 g/l, P<0.001), in TG percentage in LDL (14.4 vs. 11.4, P<0.05) and in TG percentage in HDL (10.2 vs. 8.3, P<0.05) were observed Advanced stage of HIV infection is associated with an atherogenic lipid profile including a high prevalence of sdLDL. Lopinavir/ritonavir-containing regimen accentuates the reduction of LDL size. Since fibrates decrease TG and increase LDL size, they appear as a logical option to manage HAART-induced HTG.

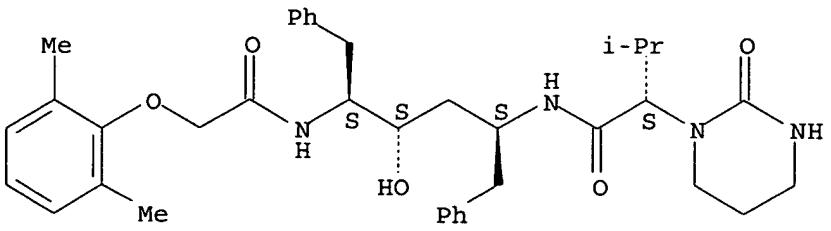
IT **369372-47-4**, Lopinavir-ritonavir mixture
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(decrease in LDL size in HIV-pos. adults before and after lopinavir/ritonavir-containing regimen)

RN 369372-47-4 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

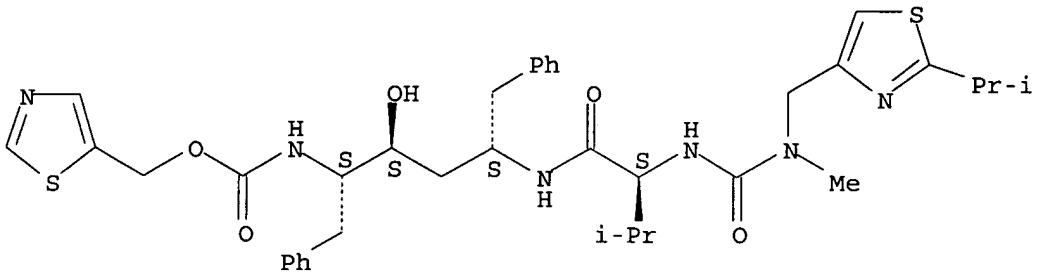
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:58128 HCAPLUS
DOCUMENT NUMBER: 138:105628
TITLE: Activated haptens comprising HIV protease inhibitor conjugates for raising antibodies useful in immunoassay
INVENTOR(S): Deras, Ina; Hui, Raymond; Sigler, Gerald F.; Huber, Erasmus J.; Von der Eltz, Herbert W.; Ghoshal, Mitali; Root, Richard Terry; Metz, Sigrun
PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany; F. Hoffmann-La Roche A.-G.
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006506	A2	20030123	WO 2002-EP7843	20020715 <--
WO 2003006506	A3	20031106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1409546	A2	20040421	EP 2002-754883		20020715
JP 2005508877	T2	20050407	~~JP 2003-512276~~		20020715
PRIORITY APPLN. INFO.:			US 2001-305192P	P	20010713
			US 2002-192052	A	20020710
			WO 2002-EP7843	W	20020715

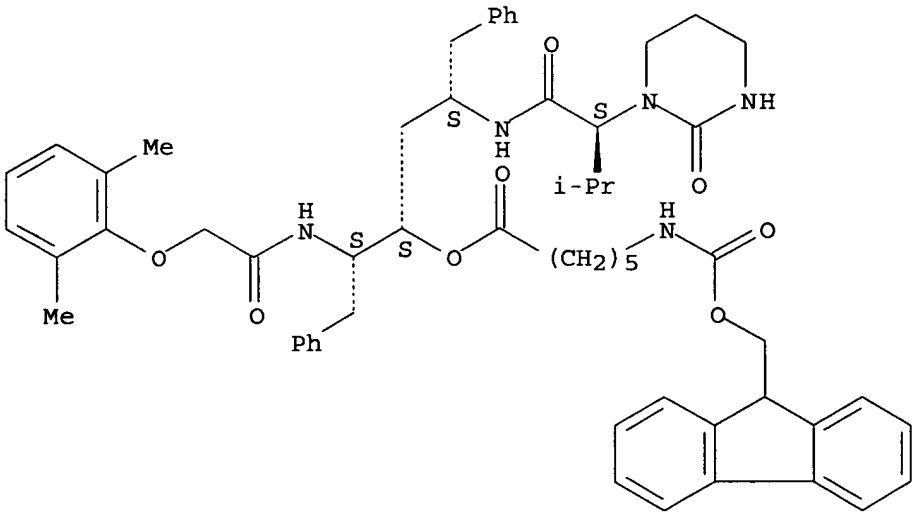
AB Activated haptens useful for generating immunogens to HIV protease inhibitors, immunogens useful for producing antibodies to HIV protease inhibitors, and antibodies and labeled conjugates useful in immunoassays for HIV protease inhibitors. The novel haptens feature an activated functionality at the central, non-terminal hydroxyl group common to all HIV protease inhibitors, e.g., saquinavir, nelfinavir, indinavir, amprenavir, ritonavir and lopinavir.

IT **485799-46-0P 485799-47-1P 485799-48-2P**
485799-49-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(activated haptens comprising HIV protease inhibitor conjugates for raising antibodies useful in immunoassay)

RN 485799-46-0 HCAPLUS

CN Hexanoic acid, 6-[[(9H-fluoren-9-ylmethoxy)carbonyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

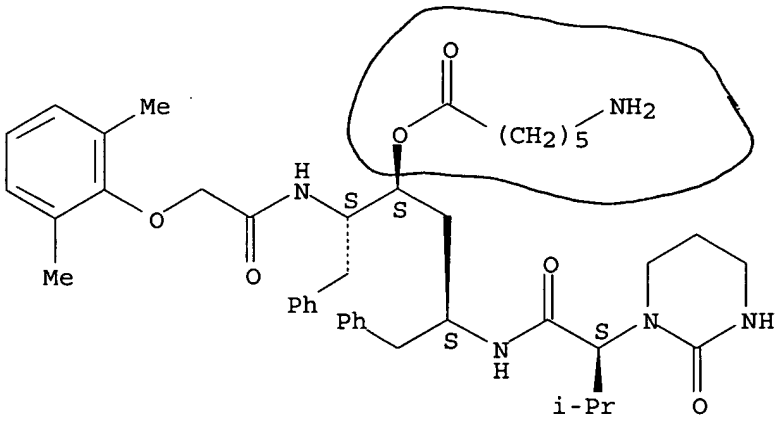
Absolute stereochemistry.



RN 485799-47-1 HCAPLUS

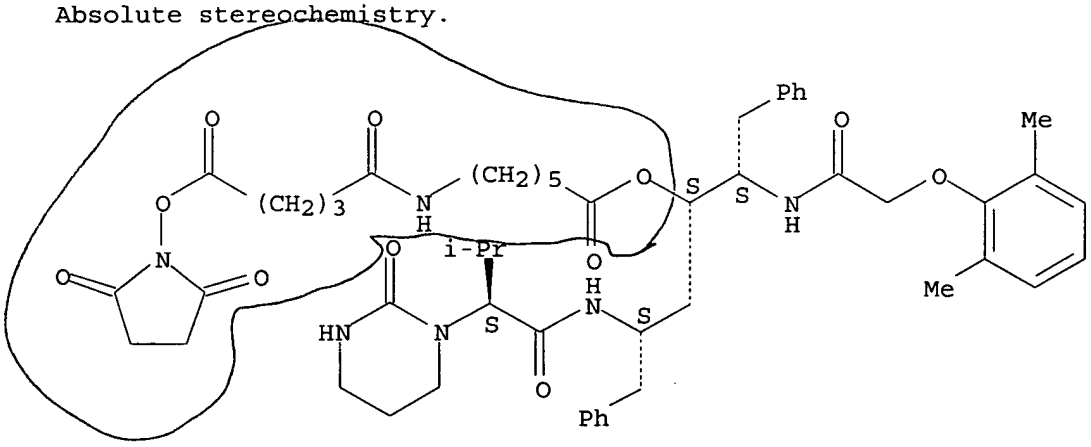
CN Hexanoic acid, 6-amino-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 485799-48-2 HCAPLUS
CN Hexanoic acid, 6-[[5-[(2,5-dioxo-1-pyrrolidinyl)oxy]-1,5-dioxopentyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

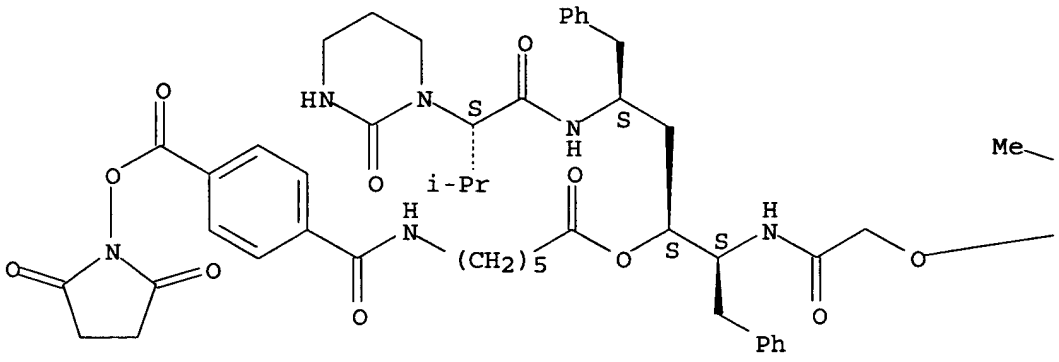
Absolute stereochemistry.



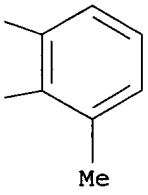
RN 485799-49-3 HCAPLUS
CN Hexanoic acid, 6-[[4-[[(2,5-dioxo-1-pyrrolidinyl)oxy]carbonyl]benzoyl]amino]-, (1S,3S)-1-[(1S)-1-[[(2,6-dimethylphenoxy)acetyl]amino]-2-phenylethyl]-3-[[(2S)-3-methyl-1-oxo-2-(tetrahydro-2-oxo-1(2H)-pyrimidinyl)butyl]amino]-4-phenylbutyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L13 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:973660 HCAPLUS
DOCUMENT NUMBER: 138:32850
TITLE: Analysis of the virological response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving lopinavir/ritonavir therapy
AUTHOR(S): Kempf, Dale J.; Isaacson, Jeffrey D.; King, Martin S.; Brun, Scott C.; Sylte, Jacquelyn; Richards, Bruce; Bernstein, Barry; Rode, Richard; Sun, Eugene
CORPORATE SOURCE: Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, USA
SOURCE: Antiviral Therapy (**2002**), 7(3), 165-174
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The virol. response of multiple protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor-naive, HIV-1-infected subjects was examined with respect to baseline viral phenotype and genotype through 72 wk of therapy with lopinavir/ritonavir plus efavirenz and nucleoside reverse transcriptase inhibitors (Study M98-957). Using a 'dropouts as censored' anal., plasma HIV RNA ≤400 copies/mL was observed in 93% (25/27), 73% (11/15) and 25% (2/8) of subjects with <10-fold,

10- to 40-fold, and >40-fold reduced susceptibility to lopinavir at baseline, resp. In addition, virol. response was observed in 91% (21/23), 71% (15/21) and 33% (2/6) of subjects with baseline lopinavir mutation score of 0-5, 6-7 and ≥8, resp. Through 72 wk, all subjects experiencing virol. failure whose baseline isolates contained six or more protease inhibitor mutations had a common genotypic pattern, with mutations at positions 82, 54 and 10, along with a median of four addnl. mutations in protease. However, an equal number of subjects with a similar genotypic pattern experienced virol. response. Further anal. revealed the baseline phenotypic susceptibility to lopinavir to be an addnl. covariate predicting response in this subset of subjects. In multivariate analyses, baseline susceptibility to lopinavir was associated with response at each time point examined (weeks 24, 48 and 72). These results provide guidance for clin. relevant interpretation of phenotypic and genotypic resistance tests when applied to lopinavir/ritonavir.

IT **369372-47-4**, Lopinavir/ritonavir mixture
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anal. of virol. response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving lopinavir/ritonavir therapy)

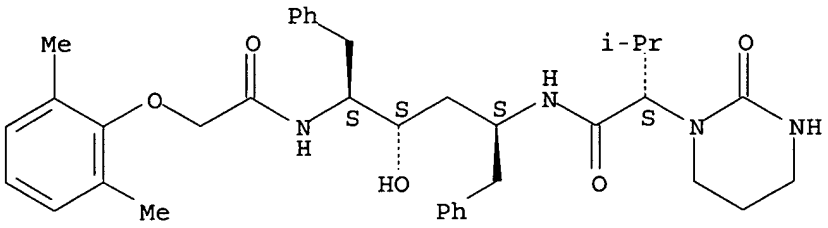
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

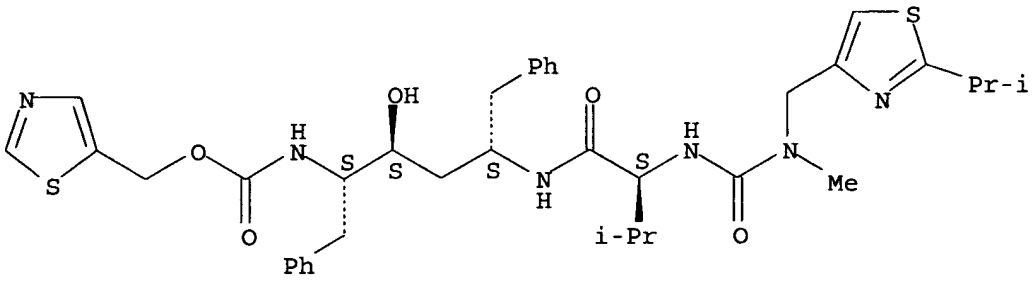
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:840545 HCAPLUS
DOCUMENT NUMBER: 139:62304
TITLE: Innovation: seventeen new molecules launched in 2001
AUTHOR(S): Anon.
CORPORATE SOURCE: Fr.
SOURCE: Info Chimie Magazine (**2002**), 441, 60-62
CODEN: ICHMFA; ISSN: 1286-0921
PUBLISHER: Societe d'Expansion Technique et Economique
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French

AB A review. From Actonel to Zyban, 17 new mols. were added to the French pharmacopiae in 2001. A result which reflects a clear slowdown in innovation.

IT **369372-47-4**, Kaletra
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new drugs launched in 2001 in France)

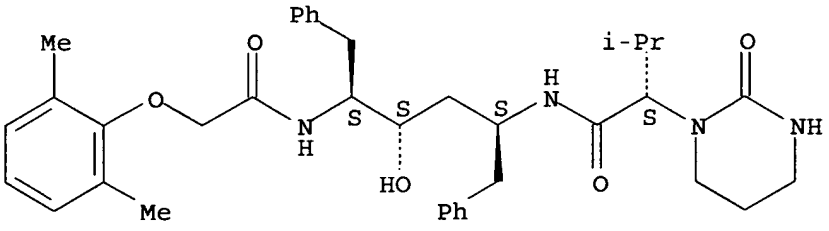
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

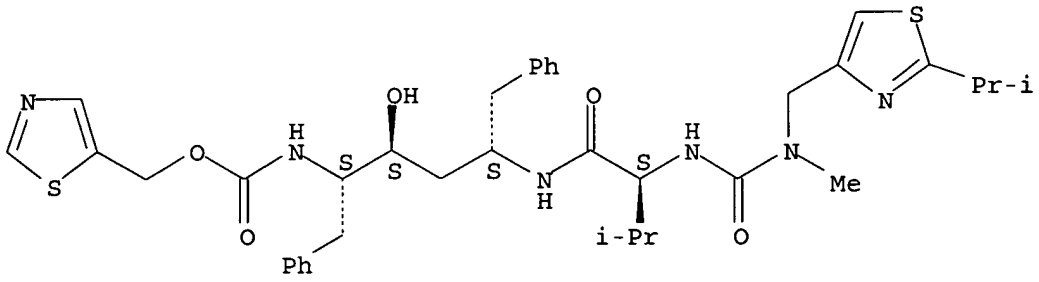
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



L13 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:580633 HCAPLUS
DOCUMENT NUMBER: 137:149667
TITLE: Kaletra (lopinavir/ritonavir)
AUTHOR(S): Corbett, Amanda H.; Lim, Michael L.; Kashuba, Angela D. M.
CORPORATE SOURCE: School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7360, USA
SOURCE: Annals of Pharmacotherapy (**2002**), 36(7/8), 1193-1203
CODEN: APHRER; ISSN: 1060-0280
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB The aim was to review the pharmacol., virol., pharmacokinetics, efficacy, safety, and clin. use of lopinavir/ritonavir (Kaletra, Abbott Labs.). English-language MEDLINE and AIDSline searches were performed (1966-July 2001) using lopinavir, ABT-378, and Kaletra as key words. Abstrs. from infectious diseases and HIV scientific meetings were identified. Abbott Labs. provided addnl. published and unpublished information. All publications, meeting abstrs., and unpublished information were reviewed and relevant items included. In vitro and preclin. studies were included as well as Phase II and III clin. trials. Lopinavir/ritonavir is a fixed-dose protease inhibitor (PI) combination used for the treatment of HIV-1 infection. Lopinavir, the active component of this combination, is extensively metabolized by CYP3A4 and produces low systemic concns. when used alone. Ritonavir potently inhibits CYP3A4 and is used to enhance the systemic exposure of lopinavir. This combination results in lopinavir concns. that greatly exceed those necessary in vitro to inhibit both wild-type and PI-resistant HIV isolates. In clin. trials with antiretroviral naive and experienced patients, lopinavir/ritonavir was effective at suppressing HIV-RNA and increasing CD4+ T cell counts. Compared with other PIs, lopinavir/ritonavir may have advantages in the areas of pharmacokinetics, efficacy, and resistance. Toxicity, drug interactions, and medication adherence are important considerations surrounding its clin. use. Lopinavir/ritonavir is an effective option for the treatment of HIV-1-infected individuals when used in combination with other antiretroviral agents. It may be used as a component of initial therapy or salvage therapy; future studies will better define its place in

therapy.

IT **369372-47-4**, Kaletra
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Kaletra (lopinavir/ritonavir) for treatment of HIV-1 infection)

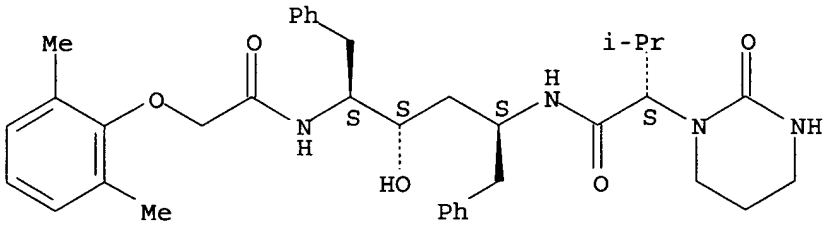
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

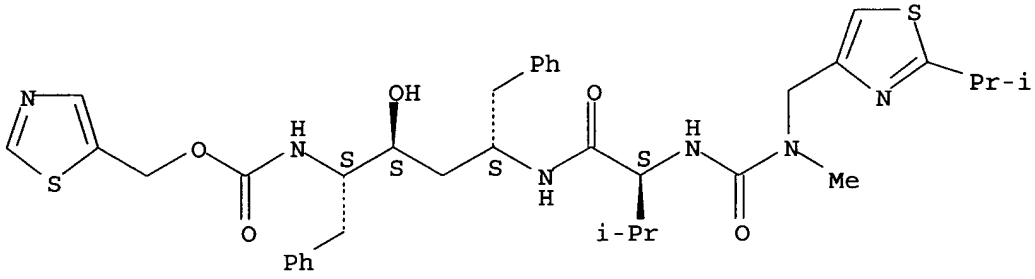
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:492873 HCAPLUS
DOCUMENT NUMBER: 137:119104
TITLE: Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection

AUTHOR(S): Walmsley, Sharon; Bernstein, Barry; King, Martin; Arribas, Jose; Beall, Gildon; Ruane, Peter; Johnson, Margaret; Johnson, David; Lalonde, Richard; Japour, Anthony; Brun, Scott; Sun, Eugene; Allworth, A. M.; Altice, F. L.; Arasteh, K.; Badley, A. D.; Barros, C.; Beal, J.; Brand, J. D.; Cameron, W.; Cimoch, P. J.; Clotet Sala, B.; Cohen, C. J.; Cooley, T. P.; Delfraissy, J.-F.; Faetkenheuer, G.; Farthing, C. F.; Feinberg, J.; Fischl, M. A.; Fisher, M.; Flepp, M.; Gallant, J.; Gathe, J. C.; Gerstoft, J.; Goldman, M.; Gonzalez-Lahoz, J. M.; Graziano, F. M.; Green, S.; Grossman, H. A.; Haas, D. W.; Haas, F. F.; Hauptman, S. P.; Hicks, C. B.; Horban, A.; Horton, J. M.; Hyslop, N. E., Jr.; Kalayjian, R. C.; Kazanjian, P. H.; Kostman, J.; Lampiris, H. W.; LaPlante, F.; Lennox, J. L.; Luskin-Hawk, R.; Mallal, S.; Mathiesen, L.; Silva de Mendonca, J.; Miao, P.; Mildvan, D.; Miller, S.; Montaner, J. S. G.; Mouton, Y.; Myers, R. A., Jr.; Pavia, A. T.; Pedersen, C.; Pierone, G., Jr.; Pollard, R. B.; Pozniak, A.; Rachlis, A. R.; Rhame, F. S.; Rubio, R.; Saimot, A. G.; Sampson, J. H.; Sanne, I.; Santana, J. L.; Seekins, D.; Sepulveda, G. E.; Sereni, D.; Sharma, S.; Sherer, R. D., Jr.; Smith, L. G.; Squires, K. E.; Staszewski, S.; Steigbigel, R. T.; Steinhart, C. R.; Stoehr, A.; Stryker, R.; Sweet, D. E.; Tashima, K. T.; Theisen, A.; Thomas, R.; Thommes, J. A.; Thompson, M. A.; Timermann, A.; Viciana, P.; Vittecoq, D.; Weber, J. N.; Weitner, D. L.; van der Westhuizen, I. P.; Wheeler, D. A.; Wright, D. P.; Yangco, B. G.
CORPORATE SOURCE: M98-863 Study Team, Toronto Hospital, Univ. Health Network, University Toronto, Toronto, ON, Can.
SOURCE: New England Journal of Medicine (**2002**), 346(26), 2039-2046
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lopinavir is a newly developed inhibitor of human immunodeficiency virus (HIV) protease that, when formulated with ritonavir, yields mean trough plasma lopinavir concns. that are at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50 %. We conducted a double-blind trial in which 653 HIV-infected adults who had not received anti-retroviral therapy for more than 14 days were randomly assigned to receive either lopinavir-ritonavir (400 mg of lopinavir plus 100 mg of ritonavir twice daily) with nelfinavir placebo or nelfinavir (750 mg three times daily) with lopinavir-ritonavir placebo. All patients also received open-label stavudine and lamivudine. The primary efficacy end points were the presence of fewer than 400 HIV RNA copies per mL of plasma at week 24 and the time to the loss of virol. response through week 48. At week 48, greater proportions of patients treated with lopinavir-ritonavir than of patients treated with nelfinavir had fewer than 400 copies of HIV RNA per mL (75 % vs. 63 %, $P < 0.001$) and fewer than 50 copies per mL (67 % vs. 52 %, $P < 0.001$). The time to the loss of virol. response was greater in the lopinavir-ritonavir group than in the nelfinavir group (hazard ratio, 2.0; 95 % confidence interval, 1.5 to 2.7; $P < 0.001$). The estimated proportion of patients with a persistent virol. response through week 48 was 84 % for patients receiving lopinavir-ritonavir and 66 % for those receiving nelfinavir. Both regimens were well tolerated, with the rate of

discontinuation related to the study drugs at 3.4 % among patients receiving lopinavir-ritonavir and 3.7 % among patients receiving nelfinavir. Among patients with more than 400 copies of HIV RNA per mL at some point from week 24 through week 48, resistance mutations in HIV protease were demonstrated in viral isolates from 25 to 76 nelfinavir-treated patients (33 %) and none of 37 patients treated with lopinavir-ritonavir ($P < 0.001$). For the initial treatment of HIV-infected adults, a combination regimen that includes lopinavir-ritonavir is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen.

IT **369372-47-4**, Kaletra
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lopinavir-ritonavir vs. nelfinavir for initial treatment of HIV infection)

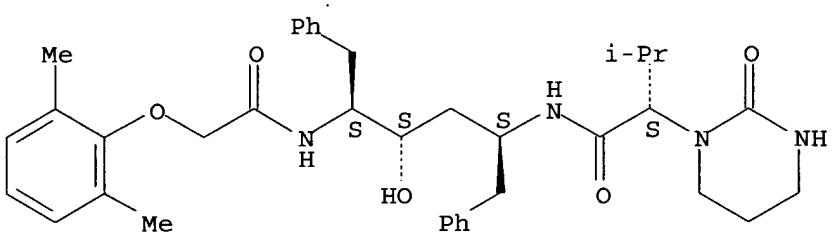
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

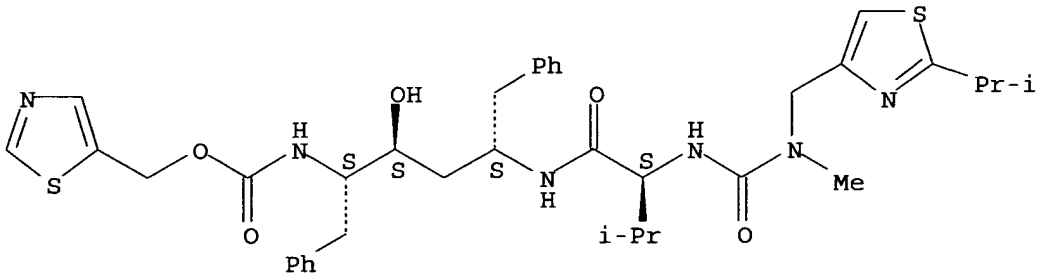
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:358148 HCAPLUS
DOCUMENT NUMBER: 137:206
TITLE: Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir-ritonavir
AUTHOR(S): Clarke, Susan; Mulcahy, Fiona; Begin, Colm; Reynolds, Helen; Boyle, Nicola; Barry, Michael; Back, David J.
CORPORATE SOURCE: Genitourinary Medicine and Infectious Disease Clinic, Liverpool, UK
SOURCE: Clinical Infectious Diseases (**2002**), 34(8), 1143-1145
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A study was designated to determine the interactions, both clin. and pharmacokinetic, between methadone and lopinavir-ritonavir. Results demonstrated a 36% reduction in the methadone area under the plasma concentration-time curve after the introduction of lopinavir-ritonavir, with no coincident symptoms of opioid withdrawal and no requirement for methadone dose adjustment.

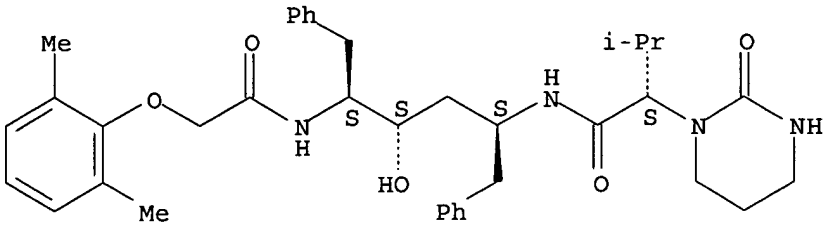
IT **369372-47-4**, Lopinavir-ritonavir mixture
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetic interaction and absence of opioid withdrawal symptoms in humans receiving methadone and protease inhibitor lopinavir-ritonavir)

RN 369372-47-4 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

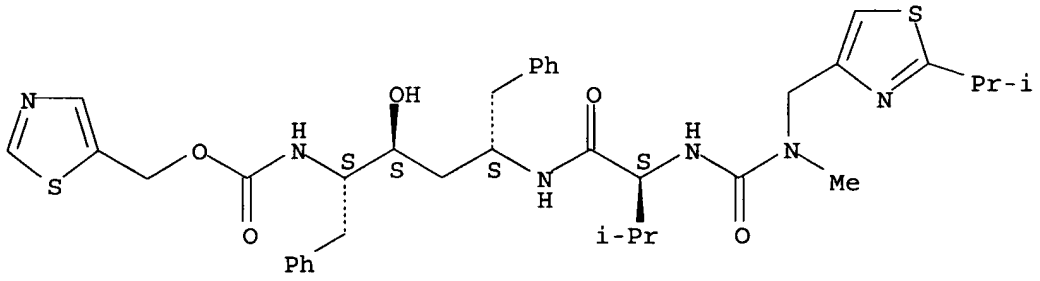
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:223196 HCAPLUS
DOCUMENT NUMBER: 136:379516
TITLE: Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients
AUTHOR(S): Benson, Constance A.; Deeks, Steven G.; Brun, Scott C.; Gulick, Roy M.; Eron, Joseph J.; Kessler, Harold A.; Murphy, Robert L.; Hicks, Charles; King, Martin; Wheeler, David; Feinberg, Judith; Stryker, Richard; Sax, Paul E.; Riddler, Sharon; Thompson, Melanie; Real, Kathryn; Hsu, Ann; Kempf, Dale; Japour, Anthony J.; Sun, Eugene
CORPORATE SOURCE: Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: Journal of Infectious Diseases (**2002**), 185(5), 599-607
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The safety and antiviral activity of lopinavir (Lpv), a protease inhibitor (PI) coformulated with ritonavir (Rtv) to enhance its pharmacokinetic properties, were evaluated in 70 patients with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels of 1000-100,000 copies/mL on a first PI-containing regimen. Patients were randomized to substitute only the PI with Lpv/Rtv, 400/100 mg or 400/200 mg twice daily. On day 15, nevirapine (200 mg 2+/day) was added, and nucleoside reverse-transcriptase inhibitors were changed. Despite a >4-fold reduction in phenotypic susceptibility to the preentry PI in 63% of patients, mean plasma HIV-1 RNA levels declined by 1.14 log10 copies/mL after 2 wk of Lpv/Rtv. At week 48, 86% of subjects receiving treatment had plasma HIV-1 RNA levels of <400 copies/mL; 76% had levels <50 HIV-1 RNA copies/mL (intent-to-treat: 70% and 60%, resp.). Mean CD4 cell counts increased by 125 cells/μL. Three patients discontinued therapy for drug-related adverse events.

IT **369372-47-4**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and antiviral activity at 48 wk of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human immunodeficiency virus type 1-infected protease inhibitor-experienced patients)

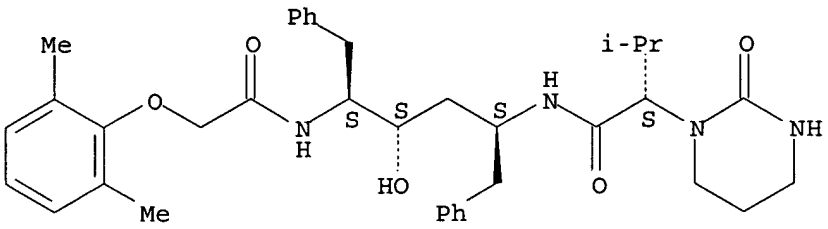
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

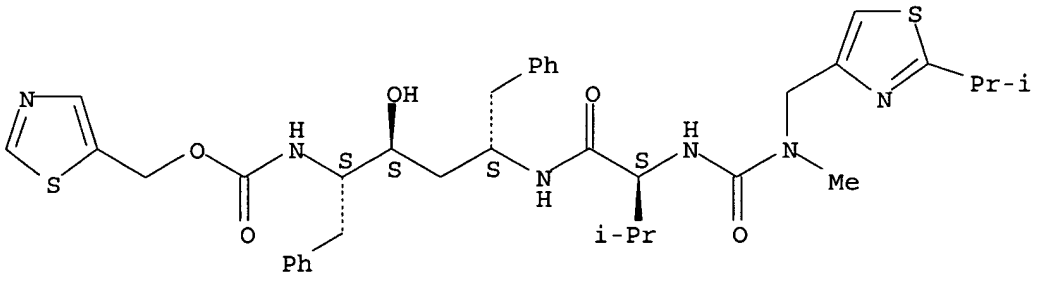
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:903574 HCAPLUS
DOCUMENT NUMBER: 136:160777
TITLE: Lopinavir-ritonavir: A new protease inhibitor

AUTHOR(S): Mangum, Eric M.; Graham, Kathleen K.
CORPORATE SOURCE: Department of Pharmacy Practice, College of Pharmacy, Nova Southeastern University, Ft. Lauderdale, FL, USA
SOURCE: Pharmacotherapy (**2001**), 21(11), 1352-1363
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Lopinavir is a new protease inhibitor that is structurally related to ritonavir. It recently was approved by the Food and Drug Administration as a coformulation with ritonavir under the brand name Kaletra. Ritonavir substantially increases lopinavir drug exposure by inhibiting cytochrome P 450 isoenzyme 3A4. Based on limited data, lopinavir-ritonavir demonstrates safety and efficacy in both antiretroviral-naive and protease inhibitor-experienced patients. It has the ability to durably suppress human immunodeficiency virus (HIV) RNA for up to 2 yr in antiretroviral-naive patients. Compared with nelfinavir, it had superior virol. control at 48 wk in antiretroviral-naive patients. Its side effects include diarrhea, abnormal stools, abdominal pain, nausea, vomiting, and asthenia. A number of patients experienced grade 3-4 laboratory abnormalities in liver function tests, cholesterol, and triglycerides while receiving this drug combination. The exact resistance patterns of lopinavir-ritonavir are unknown, but the Department of Health and Human Services strongly recommends it for the initial treatment of HIV-infected adults and adolescents.

IT **369372-47-4**, Kaletra
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lopinavir-ritonavir combination (Kaletra): new protease inhibitor for HIV-infected humans)

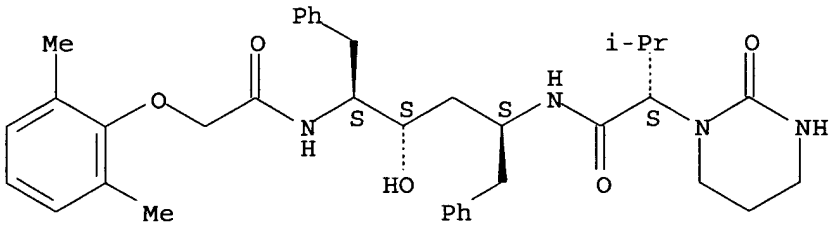
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

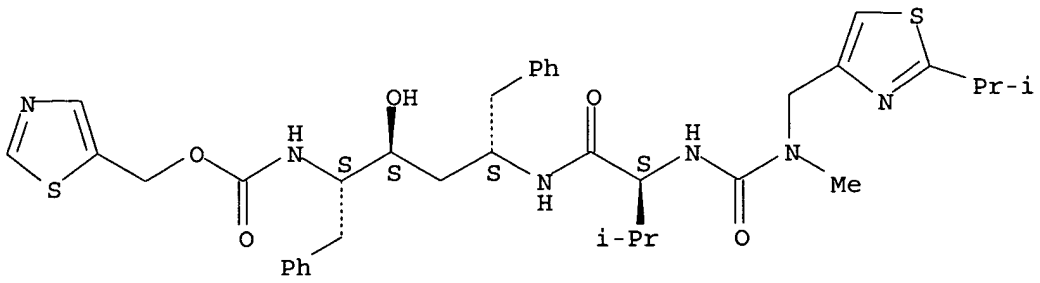
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:776234 HCAPLUS
DOCUMENT NUMBER: 136:63530
TITLE: Simultaneous determination of the new HIV protease inhibitor lopinavir (ABT 378) and of indinavir, amprenavir, saquinavir, ritonavir (ABT 538) and nelfinavir in human plasma by gradient HPLC
AUTHOR(S): Kuschak, Dieter; Mauss, Stefan; Schmutz, Gunther; Gantke, Beate; Nemes, Gertrude; Schauseil, Stephan; Nemes, Paul; Kux, Michael; Gehrt, Andreas
CORPORATE SOURCE: Medical Laboratories Dusseldorf, Dusseldorf, Germany
SOURCE: Clinical Laboratory (Heidelberg, Germany) (2001), 47(9+10), 471-477
CODEN: CLLAFP; ISSN: 0941-2131
PUBLISHER: Verlag Klinisches Labor
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protease inhibitors are known by their inhibition of a viral protease that leads to production of immature and non-infectious virus particles. The novel protease inhibitor KALETRA is a co-formulation of lopinavir and ritonavir. Ritonavir reduces the metabolization of lopinavir by the cytochrome P 450 3A4 isoenzyme which leads to markedly increased plasma levels of lopinavir. A new rapid and sensitive HPLC method for the simultaneous determination of lopinavir, indinavir, amprenavir, saquinavir, ritonavir and nelfinavir in human plasma has been developed. An aliquot of 500 μl plasma, spiked with internal standard, was extracted with 500 μl 0.1 M ammonium hydroxide solution and 5 mL tert.-Bu ether. After drying under a nitrogen stream, the residue was redissolved in an eluent consisting of 50 mM phosphate buffer, pH 5.40 and acetonitrile (50:50, volume/volume). Chromatog. separation was accomplished on a C-18 column using a non-linear gradient elution and UV detection at 215 nm.

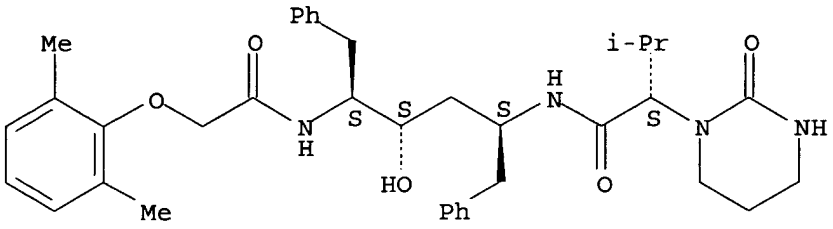
IT **369372-47-4**, KALETRA
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(determination of new HIV protease inhibitor lopinavir (ABT 378) and of indinavir, amprenavir, saquinavir, ritonavir (ABT 538) and nelfinavir in human plasma by gradient high-performance liquid chromatog. (HPLC))

RN 369372-47-4 HCAPLUS
CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

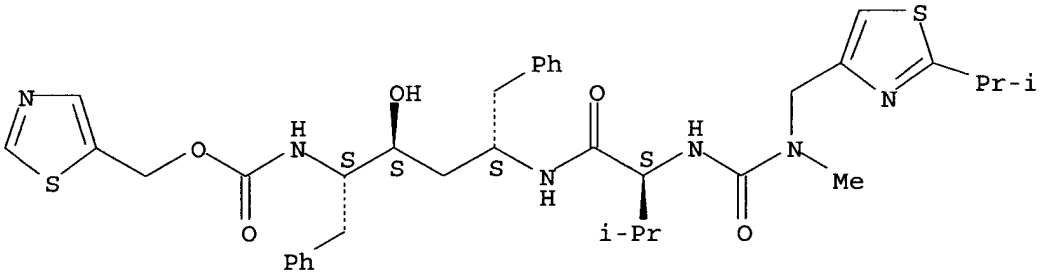
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:493738 HCAPLUS
DOCUMENT NUMBER: 135:335048
TITLE: FDA new drug approvals in 2000
AUTHOR(S): Zhao, Kang; Reiner, John; Xie, Weilin
CORPORATE SOURCE: GNF, San Diego, CA, 92121, USA
SOURCE: Frontiers of Biotechnology & Pharmaceuticals (**2001**), 2, 329-349
CODEN: FBPRBL
PUBLISHER: Science Press New York Ltd.
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 13 refs., outlines the 26 new drug entities that have been approved by the FDA in 2000. These therapeutics are grouped into four areas coded: (A) neurotransmitter analogs, (B) anti-ulcer and antiinflammation agents, (C) hormone-related drugs, and (D) anti-infectious drugs and miscellaneous mols. The synopsis for each compound includes description of the drug's benefits for a medical need, a mode of action, a chemical structure, and in most cases an abbreviated pathway outlining how the drug is synthesized.

IT **369372-47-4**, Lopinavir-ritonavir mixture
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FDA new drug approvals in 2000)

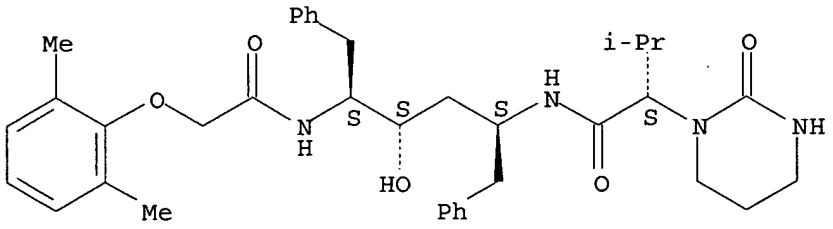
RN 369372-47-4 HCAPLUS

CN 2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (5S,8S,10S,11S)-, mixt. with (αS)-N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 192725-17-0
CMF C37 H48 N4 O5

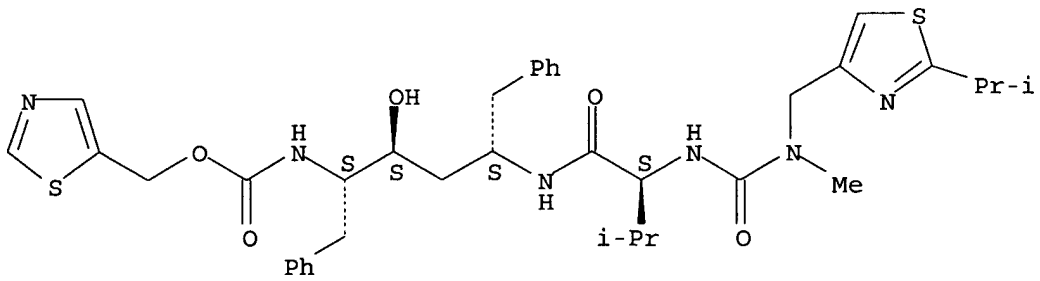
Absolute stereochemistry.



CM 2

CRN 155213-67-5
CMF C37 H48 N6 O5 S2

Absolute stereochemistry.



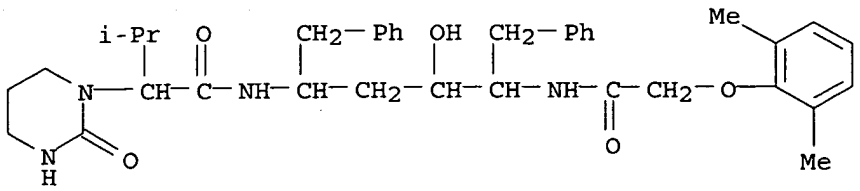
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:41866 HCAPLUS
DOCUMENT NUMBER: 130:246231
TITLE: In vitro metabolism of the HIV-1 protease inhibitor ABT-378: species comparison and metabolite identification
AUTHOR(S): Kumar, Gondi N.; Jayanti, Venkata; Lee, Ronald D.; Whittern, David N.; Uchic, John; Thomas, Samuel; Johnson, Paulette; Grabowski, Brian; Sham, Hing; Betebenner, David; Kempf, Dale J.; Denissen, Jon F.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA
SOURCE: Drug Metabolism and Disposition (**1999**), 27(1), 86-91
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HIV protease inhibitor ABT-378 was metabolized very extensively and rapidly by liver microsomes from mouse, rat, dog, monkey, and humans. The rates of NADPH-dependent metabolism of ABT-378 ranged from 2.39 to 9.80 nmol·mg microsomal protein-1·min-1, with monkey liver microsomes exhibiting the highest rates of metabolism ABT-378 was metabolized to 12 metabolites (M-1 to M-12), which were characterized by mass and NMR spectroscopy. The metabolite profile of ABT-378 in liver microsomes from all five species was similar, except that the mouse liver microsomes did not form M-9, a minor secondary metabolite. The predominant site of metabolism was the cyclic urea moiety of ABT-378. In all five species, the major metabolites were M-1 (4-oxo-ABT-378) and M-3 and M-4 (4-hydroxy-ABT-378). Metabolite M-2 (6-hydroxy-ABT-378) was formed by rodents at a faster rate than by dog, monkey, and human liver microsomes. Metabolites M-5 to M-8 were identified as monohydroxylated derivs. of ABT-378. Metabolites M-9 and M-10 were identified as hydroxylated products of M-1. Metabolites M-11 and M-12 were identified as dihydroxylated derivs. of ABT-378. The metabolite profile in human hepatocytes and liver slices was similar to that of human liver microsomes. The results of the current study indicate that ABT-378 is highly susceptible to oxidative metabolism in vitro, and possibly in vivo, in humans.

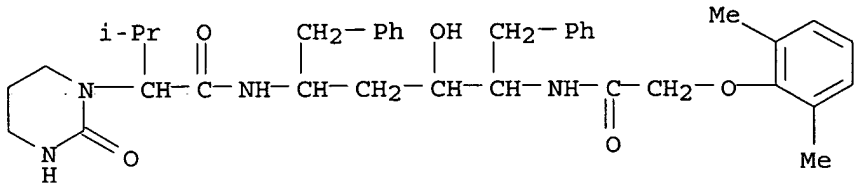
IT **221554-68-3 221555-19-7**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(In vitro metabolism of HIV-1 protease inhibitor ABT-378 in relation to species comparison and metabolite identification in human and laboratory animal liver microsomes)

RN 221554-68-3 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, monohydroxy deriv., (αS)- (9CI) (CA INDEX NAME)



D1—OH

RN 221555-19-7 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethoxyphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, monohydroxy deriv., (αS)- (9CI) (CA INDEX NAME)



D1—OH

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que stat l15
L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON 192725-17-0
L14 541 SEA FILE=HCAPLUS ABB=ON PLU=ON L9
L15 216 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 AND PY<2004

=> d l15 ibib abs hitstr 200-216

L15 ANSWER 200 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:819251 HCAPLUS
DOCUMENT NUMBER: 132:59139
TITLE: Use of 3'-azido-2',3'-dideoxyuridine in combination with further anti-HIV drugs for the manufacture of a medicament for the treatment of HIV infection
INVENTOR(S): Schinazi, Raymond; Bryant, Martin L.; Myers, Maureen W.
PATENT ASSIGNEE(S): Emory University, USA; Novirio Pharmaceuticals Ltd.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966936	A1	19991229	WO 1999-US14329	19990624 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335617	AA	19991229	CA 1999-2335617	19990624 <--
AU 9947162	A1	20000110	AU 1999-47162	19990624 <--
US 6194391	B1	20010227	US 1999-339133	19990624 <--
EP 1089741	A1	20010411	EP 1999-930672	19990624 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO				
BR 9911457	A	20011211	BR 1999-11457	19990624 <--
US 2001009906	A1	20010726	US 2001-793346	20010226 <--
US 6602664	B2	20030805		

PRIORITY APPLN. INFO.:		
US 1998-90552P	P	19980624
US 1999-132126P	P	19990430
US 1999-339133	A1	19990624
WO 1999-US14329	W	19990624

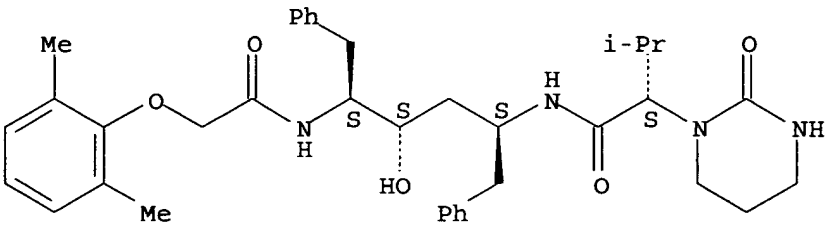
AB It has been discovered that 3'-azido-2',3'-dideoxyuridine (CS-87) induces a transient mutation in HIV-1 at the 70th codon (K to R, i.e., lysine to arginine) of the reverse transcriptase region of the virus. Based on this discovery, a method and composition for treating HIV is provided that includes administering CS-87 or its pharmaceutically acceptable salt or prodrug to a human in need of therapy in combination or alternation with a drug that induces a mutation in HIV-1 at a location other than the 70th codon of the reverse transcriptase region. This invention can be practiced by referring to the published mutation patterns for known anti-HIV drugs, or by determining the mutation pattern for a new drug.

IT **192725-17-0**, ABT-378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(azidodideoxyuridine in combination with other anti-HIV drugs for treatment of HIV infection)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



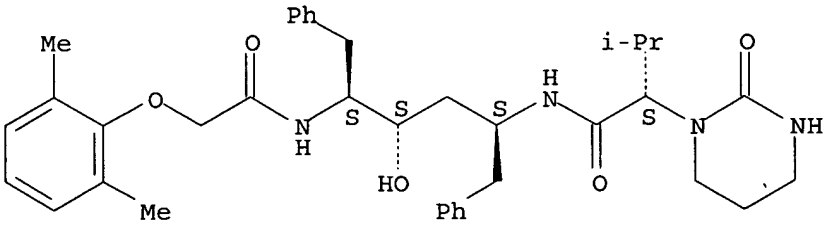
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 201 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:750592 HCAPLUS
DOCUMENT NUMBER: 132:141
TITLE: Stavudine, lamivudine plus novel protease inhibitor therapy in antiretroviral-naive HIV-infected individuals treated for 24 weeks
AUTHOR(S): Murphy, Robert L.
CORPORATE SOURCE: HIV Treatment Unit, Northwestern University Medical School, Chicago, IL, USA
SOURCE: Antiviral Therapy (**1999**), 4(Suppl. 3), 85-87
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Preliminary results are presented from a dose-comparison trial of the regimen stavudine/lamivudine plus the novel protease inhibitor, ABT-378/ritonavir, given to 101 antiretroviral-naive, human immunodeficiency virus (HIV)-infected subjects for ≥24 wk. The HIV-1 RNA had decreased to <400 copies/mL in 94% of patients and CD4 cell count had increased by approx. 160 cells/mm3 at 24 wk. The regimen was well tolerated and merits further study.

IT **192725-17-0**, ABT-378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stavudine, lamivudine plus novel protease inhibitor therapy in antiretroviral-naive HIV-infected humans treated for 24 wk)
RN 192725-17-0 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 202 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:614877 HCAPLUS
DOCUMENT NUMBER: 131:252542
TITLE: HIV protease inhibitor prodrugs for improved bioavailability and delivery to the central nervous system
INVENTOR(S): Vierling, Pierre; Guedj, Roger; Farese di Giorgio, Andrey; Greiner, Jacques; Rouquayrol, Marielle

PATENT ASSIGNEE(S): Universite de Nice Sophia Antipolis, Fr.
SOURCE: Fr. Demande, 28 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2773994	A1	19990730	FR 1998-728	19980123 <--
FR 2773994	B1	20021011		

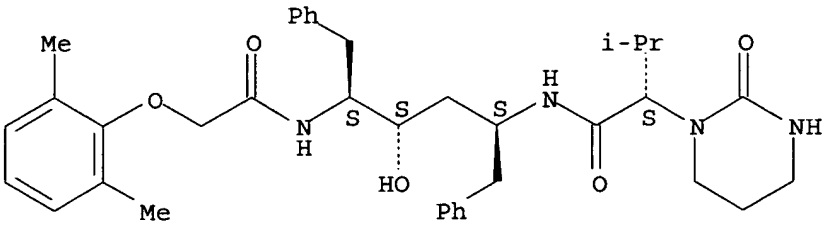
PRIORITY APPLN. INFO.: FR 1998-728 19980123
OTHER SOURCE(S): MARPAT 131:252542

AB HIV protease inhibitor prodrugs are prepared for improved bioavailability and and affinity and or delivery in the central nervous system (CNS). The prodrugs of the invention are derivs. of known anti-proteases (saquinavir, indinavir, etc.) which are (a)rendered more lipophilic by coupling with e.g. cholesterol, (b) coupled with a transporter substrate (e.g. an amino acid), or (c) rendered more hydrophilic via coupling with a polyethylene glycol. Preparation and testing of saquinavir and indinavir derivs. are described.

IT **192725-17-0D**, ABT-378, prodrug derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV protease inhibitor prodrugs for improved bioavailability and delivery to the CNS)

RN 192725-17-0 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



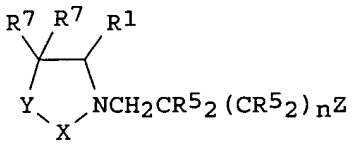
L15 ANSWER 203 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:561585 HCAPLUS
DOCUMENT NUMBER: 131:185247
TITLE: Preparation of heterocyclylhydroxyalkanamides and related compounds as aspartyl protease inhibitors
INVENTOR(S): Tung, Roger Dennis; Salituro, Francesco Gerald; Deininger, David D.; Bhisetti, Govinda Rao; Baker, Christopher Todd; Spaltenstein, Andrew
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: U.S., 69 pp., Cont.-in-part of U.S. Ser. No. 592,777.
CODEN: USXXAM
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5945413	A	19990831	US 1996-724563	19960930 <--
US 5883252	A	19990316	US 1996-592777	19960126 <--
CA 2243121	AA	19970731	CA 1997-2243121	19970122 <--
WO 9727180	A1	19970731	WO 1997-US1610	19970122 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9717580	A1	19970820	AU 1997-17580	19970122 <--
AU 709239	B2	19990826		
EP 882022	A1	19981209	EP 1997-904911	19970122 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9707086	A	19990413	BR 1997-7086	19970122 <--
JP 2000501111	T2	20000202	JP 1997-527124	19970122 <--
ZA 9700613	A	19970730	ZA 1997-613	19970124 <--
AP 844	A	20000609	AP 1997-961	19970124 <--
W: BW, GM, GH, KE, LS, MW, SD, SZ, UG, ZM, ZW				
NO 9803435	A	19980921	NO 1998-3435	19980724 <--

PRIORITY APPLN. INFO.:	US 1996-592777	A2	19960126
	US 1996-724563	A	19960930
	WO 1997-US1610	W	19970122

OTHER SOURCE(S): MARPAT 131:185247
GI



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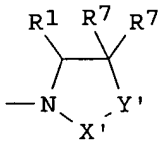
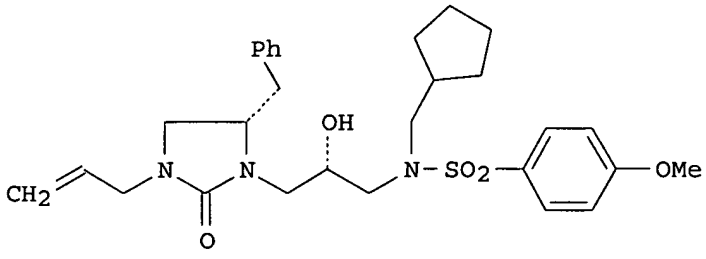


II



III

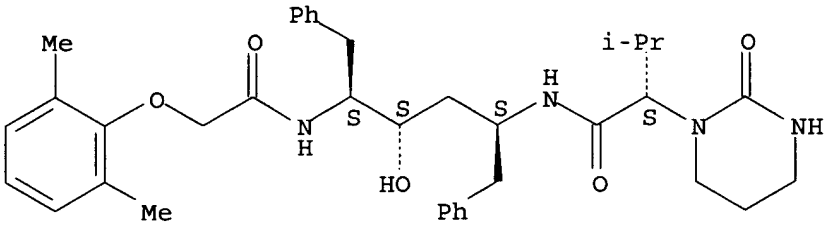
AB Title compds. I [Z = (Q)rR1X'R4, fragment II, etc., which may be fused with R6; X, X' = CO, COCO, SO, SO2; Y, Y' = (CR22)p, NR2, (CR22)pM, NR2CH2; Q = CH, N; R1, R2 = H, R6, alkyl, alkenyl, alkynyl, (fused) cycloalkyl, cycloalkenyl, etc.; R4 = (substituted) OR9, XR9, NR92, R6, alkyl, alkenyl, (fused) cycloalkyl, cycloalkenyl, etc.; R5 = H, OH, O, R1; R6 = (substituted) aryl, carbocyclyl, heterocyclyl; R7 = H, OH, O; R9 = H, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl, heterocyclylalkyl; M = NH, NR2, O, S, SO, SO2; n = 1, 2; r = 0-2] were prepared for use as aspartyl protease inhibitors. Thus, compound II (preparation given) inhibited HIV aspartyl protease with Ki = 160 nM.

IT **192725-17-0**, Abt 378
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of heterocyclylhydroxyalkanamides and related compds. as aspartyl protease inhibitors)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 204 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:494357 HCAPLUS
DOCUMENT NUMBER: 131:266510
TITLE: Potent inhibition of the cytochrome P-450 3A-mediated human liver microsomal metabolism of a novel HIV protease inhibitor by ritonavir: a positive drug-drug interaction
AUTHOR(S): Kumar, Gondi N.; Dykstra, Jennifer; Roberts, Ellen M.; Jayanti, Venkata K.; Hickman, Dean; Uchic, John; Yao, Ye; Surber, Bruce; Thomas, Samuel; Granneman, G. Richard
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Drug Metabolism and Disposition (**1999**), 27(8), 902-908
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ABT-378 is a potent in vitro inhibitor of the HIV protease and is currently being developed for coadministration with another HIV protease

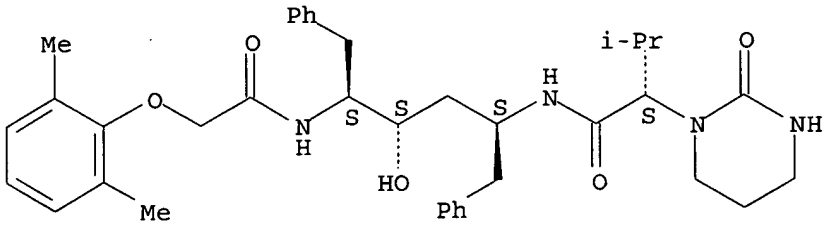
inhibitor, ritonavir, as an oral therapeutic treatment for HIV infection. In the present study, the effect of ritonavir, a potent inhibitor of cytochrome P 450 (CYP) 3A, on the in vitro metabolism of ABT-378 was examined Furthermore, the effect of ABT-378-ritonavir combinations on several CYP-dependent monooxygenase activities in human liver microsomes was also examined ABT-378 was found to undergo NADPH- and CYP3A4/5-dependent metabolism to three major metabolites, M-1 (4-oxo) and M-3/M-4 (4-hydroxy epimers), as well as several minor oxidative metabolites in human liver microsomes. The mean apparent Km and Vmax values for the metabolism of ABT-378 by human liver microsomes were 6.8 ± 3.6 μM and 9.4 ± 5.5 nmol of ABT-378 metabolized/mg protein/min, resp. Ritonavir inhibited human liver microsomal metabolism of ABT-378 potently (K1 = 0.013 μM). The combination of ABT-378 and ritonavir was much weaker in inhibiting CYP-mediated biotransformations than ritonavir alone, and the inhibitory effect appears to be primarily due to the ritonavir component of the combination. The ABT-378-ritonavir combinations (at 3:1 and 29:1 ratios) inhibited CYP3A (IC50 = 1.1 and 4.6 μM), albeit less potently than ritonavir (IC50 = 0.14 μM). Metabolic reactions mediated by CYP1A2, CYP2A6, and CYP2E1 were not affected by the ABT-378-ritonavir combinations. The inhibitory effects of ABT-378-ritonavir combinations on CYP2B6 (IC50 = >30 μM), CYP2C9 (IC50 = 13.7 and 23.0 μM), CYP2C19 (IC50 = 28.7 and 38.0 μM), and CYP2D6 (IC50 = 13.5 and 29.0 μM) were marginal and are not likely to produce clin. significant drug-drug interactions.

IT **192725-17-0**, ABT-378
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ritonavir inhibition of cytochrome P 450 CYP3A-mediated human liver microsomal metabolism of HIV protease inhibitor ABT-378 as pos. drug-drug interaction)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

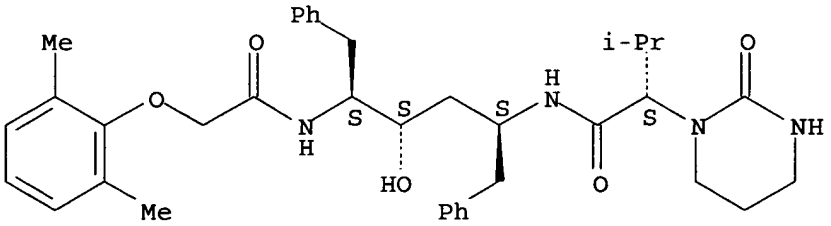


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 205 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:477765 HCAPLUS
DOCUMENT NUMBER: 131:237541
TITLE: JE-2147: a dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1
AUTHOR(S): Yoshimura, Kazuhisa; Kato, Ryohei; Yusa, Keisuke; Kavlick, Mark F.; Maroun, Victor; Nguyen, Aline; Mimoto, Tsutomu; Ueno, Takamasa; Shintani, Makoto; Falloon, Judith; Masur, Henry; Hayashi, Hideya;

Erickson, John; Mitsuya, Hiroaki
CORPORATE SOURCE: Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1999**), 96(15), 8675-8680
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors designed, synthesized, and identified JE-2147, an allophenylnorstatine-containing dipeptide HIV protease inhibitor (PI), which is potent against a wide spectrum of HIV-1, HIV-2, simian immunodeficiency virus, and various clin. HIV-1 strains in vitro. Drug-resistant clin. HIV-1 strains, isolated from seven patients who had failed 9-11 different anti-HIV therapeutics after 32-83 mo, had a variety of drug-resistance-related amino acid substitutions and were highly and invariably resistant to all of the currently available anti-HIV agents. JE-2147 was, however, extremely potent against all such drug-resistant strains, with IC50 values ranging from 13-41 nM (2-fold changes in IC50 compared with that of wild-type HIV-1). The emergence of JE-2147-resistant HIV-1 variants in vitro was substantially delayed compared with that of HIV-1 resistant to another allophenylnorstatine-containing compound, KNI-272, and other related PIs. Structural anal. revealed that the presence of a flexible P2' moiety is important for the potency of JE-2147 toward wild-type and mutant viruses. These data suggest that the use of flexible components may open a new avenue for designing PIs that resist the emergence of PI-resistant HIV-1. Further development of JE-2147 for treating patients harboring multi-PI-resistant HIV-1 is warranted.
IT **192725-17-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JE-2147 as dipeptide HIV protease inhibitor that potently inhibits multi-protease inhibitor-resistant HIV-1)
RN 192725-17-0 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

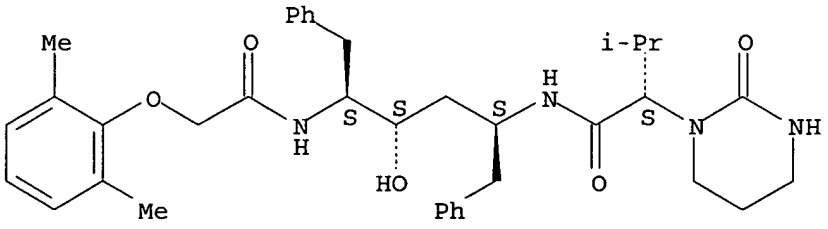
L15 ANSWER 206 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:413568 HCAPLUS
DOCUMENT NUMBER: 131:82457
TITLE: ABT-378 Abbott Laboratories
AUTHOR(S): Wlodawer, Alexander
CORPORATE SOURCE: Macromolecular Structure Laboratory, National Cancer Institute ABL-Basic Research Program, Frederick, MD, 21702, USA
SOURCE: Current Opinion in Anti-Infective Investigational Drugs (**1999**), 1(2), 246-250
CODEN: COADFY; ISSN: 1464-8458
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with .apprx.40 refs. Abbott is developing ABT-378, ~~a second~~ generation HIV protease inhibitor, as a potential treatment for HIV infection. The compound is in early phase II clin. trials [283199]. One of several trials planned is a dose-ranging phase II trial studying the effect of a twice-daily regimen of ABT-378 in combination with d4T and 3TC [310177]. Preliminary phase II data demonstrated that ABT-378 is well-tolerated. Participants in the controlled study were treated for 24 wk and had not previously received antiretroviral treatment. Over 93% of antiretroviral-naive patients (70 out of 74) showed HIV RNA levels of less than 400 copies/mL after 20 to 24 wk of treatment with ABT-378/ritonavir. Analysts predict a US filing in 2000, with launch of the drug in early 2001 [318619,318933].

IT **192725-17-0**, ABT-378
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(ABT-378 for treatment of HIV infection in humans)

RN 192725-17-0 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 207 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:393986 HCAPLUS
DOCUMENT NUMBER: 131:59143
TITLE: Preparation of peptide analogs as retroviral protease inhibitors
INVENTOR(S): Sham, Hing Leung; Norbeck, Daniel W.; Chen, Xiaoqi; Betebenner, David A.

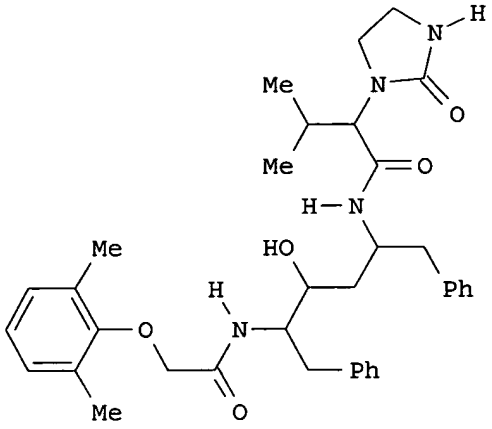
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 44 pp., Cont.-in-part of U.S. Ser. No. 572,226, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5914332	A	19990622	US 1996-753201	19961121 <--
CA 2238978	AA	19970619	CA 1996-2238978	19961206 <--
CA 2238978	C	20010515		
CA 2285119	AA	19970619	CA 1996-2285119	19961206 <--
CA 2285119	C	20050920		
CA 2509505	AA	19970619	CA 1996-2509505	19961206 <--
WO 9721685	A1	19970619	WO 1996-US20440	19961206 <--
W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NZ				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9713422	A1	19970703	AU 1997-13422	19961206 <--
AU 725369	B2	20001012		
EP 882024	A1	19981209	EP 1996-944941	19961206 <--
EP 882024	B1	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1208405	A	19990217	CN 1996-199904	19961206 <--
JP 2000502085	T2	20000222	JP 1997-522278	19961206 <--
JP 3170292	B2	20010528		
JP 2001058979	A2	20010306	JP 2000-190510	19961206 <--
EP 1170289	A2	20020109	EP 2001-124290	19961206 <--
EP 1170289	A3	20021113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
AT 212986	E	20020215	AT 1996-944941	19961206 <--
PT 882024	T	20020731	PT 1996-944941	19961206 <--
ES 2173341	T3	20021016	ES 1996-944941	19961206 <--
EP 1295874	A2	20030326	EP 2002-26856	19961206 <--
EP 1295874	A3	20030402		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
NZ 510329	A	20040227	NZ 1996-510329	19961206
CZ 293650	B6	20040616	CZ 2000-2210	19961206
CZ 294246	B6	20041110	CZ 1998-1762	19961206
NZ 510328	A	20050128	NZ 1996-510328	19961206
NZ 338003	A	20050826	NZ 1996-338003	19961206
ZA 9610475	A	19970731	ZA 1996-10475	19961212 <--
TW 494097	B	20020711	TW 1997-86101654	19970213 <--
US 6284767	B1	20010904	US 1998-207873	19981208 <--
HK 1016585	A1	20020809	HK 1999-101462	19990409 <--
US 6313296	B1	20011106	US 2000-511390	20000223 <--
US 2002004503	A1	20020110	US 2001-837280	20010418 <--
US 6472529	B2	20021029		
US 2003100755	A1	20030529	US 2002-280652	20021025 <--

PRIORITY APPLN. INFO.:		
US 1995-572226	B2	19951213
US 1996-753201	A	19961121
US 1996-754687	A	19961121
CA 1996-2238978	A3	19961206
CA 1996-2285119	A3	19961206
EP 1996-943605	A3	19961206
EP 1996-944941	A3	19961206
JP 1997-522278	A3	19961206

WO 1996-US20440 W 19961206
US 1998-207873 A3 19981208
US 2001-837280 A3 20010418

OTHER SOURCE(S): MARPAT 131:59143
GI



II

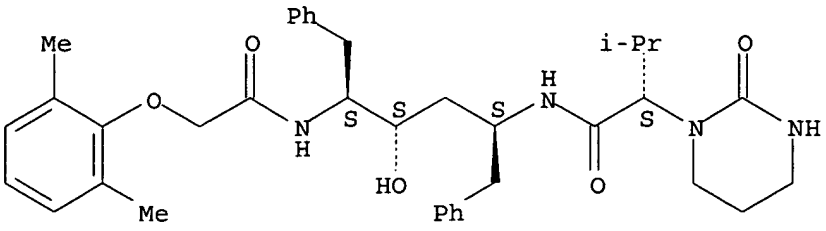
AB R4Z1CONHCHR1CH(OH)CH2CHR2NHCOCHR3R5 [I; R1,R2 = lower alkyl, cycloalkylalkyl, arylalkyl; R3 = lower alkyl, hydroxyalkyl, cycloalkylalkyl; R4 = aryl, heterocyclyl; R5 = N-attached (thi)oxo- or iminoazacycloalkyl; Z1 = Z, O, S, (alkyl)imino, OZ, ZO, NHZ, etc.; Z = alkylene] were prepared Thus, title compound (S,S,S)-II was prepared in 8 steps from L-phenylalanine. Data for biol. activity of I were given.

IT **192725-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide analogs as retroviral protease inhibitors for inhibiting HIV infection)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

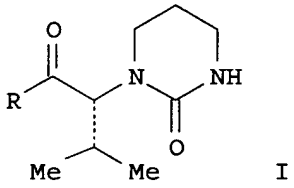
Absolute stereochemistry.



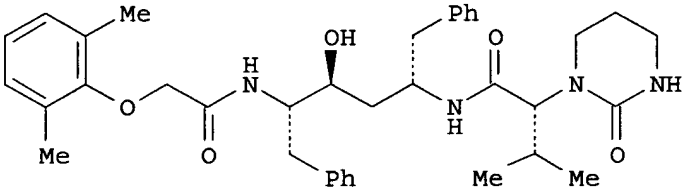
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 208 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:129353 HCAPLUS
DOCUMENT NUMBER: 130:267737
TITLE: Synthesis of ABT-378, an HIV Protease Inhibitor Candidate: Avoiding the Use of Carbodiimides in a Difficult Peptide Coupling
AUTHOR(S): Stoner, Eric J.; Stengel, Peter J.; Cooper, Arthur J.
CORPORATE SOURCE: Process Research and Development, Abbott Laboratories, North Chicago, IL, 60064, USA
SOURCE: Organic Process Research & Development (**1999**), 3(2), 145-148
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:267737
GI



I



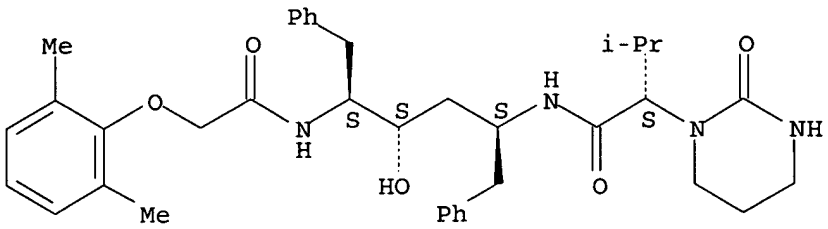
II

AB An alternative to carbodiimide-mediated peptide coupling protocols has been developed for carboxylic acid I (R = OH) prone to decomposition by polymerization
This method, involving the in situ generation of acyl imidazolide I (R = imidazolyl) from acid chloride I (R = Cl), has been applied to the preparation of a lead clin. HIV protease inhibitor candidate, ABT-378 (II). The nature of the polymerization and optimization of the new reaction conditions are
presented.

IT **192725-17-0P**, ABT 378
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation HIV protease inhibitor candidate ABT 378 via acyl imidazolide in difficult peptide coupling)

RN 192725-17-0 HCAPLUS
CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 209 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:41866 HCAPLUS
DOCUMENT NUMBER: 130:246231
TITLE: In vitro metabolism of the HIV-1 protease inhibitor ABT-378: species comparison and metabolite identification
AUTHOR(S): Kumar, Gondi N.; Jayanti, Venkata; Lee, Ronald D.; Whittern, David N.; Uchic, John; Thomas, Samuel; Johnson, Paulette; Grabowski, Brian; Sham, Hing; Betebenner, David; Kempf, Dale J.; Denissen, Jon F.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA
SOURCE: Drug Metabolism and Disposition (**1999**), 27(1), 86-91
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HIV protease inhibitor ABT-378 was metabolized very extensively and rapidly by liver microsomes from mouse, rat, dog, monkey, and humans. The rates of NADPH-dependent metabolism of ABT-378 ranged from 2.39 to 9.80 nmol·mg microsomal protein-1·min-1, with monkey liver microsomes exhibiting the highest rates of metabolism ABT-378 was metabolized to 12 metabolites (M-1 to M-12), which were characterized by mass and NMR spectroscopy. The metabolite profile of ABT-378 in liver microsomes from all five species was similar, except that the mouse liver microsomes did not form M-9, a minor secondary metabolite. The predominant site of metabolism was the cyclic urea moiety of ABT-378. In all five species, the major metabolites were M-1 (4-oxo-ABT-378) and M-3 and M-4 (4-hydroxy-ABT-378). Metabolite M-2 (6-hydroxy-ABT-378) was formed by rodents at a faster rate than by dog, monkey, and human liver microsomes. Metabolites M-5 to M-8 were identified as monohydroxylated derivs. of ABT-378. Metabolites M-9 and M-10 were identified as hydroxylated products of M-1. Metabolites M-11 and M-12 were identified as dihydroxylated derivs. of ABT-378. The metabolite profile in human hepatocytes and liver slices was similar to that of human liver microsomes. The results of the current study indicate that ABT-378 is highly susceptible to oxidative metabolism in vitro, and possibly in vivo, in humans.

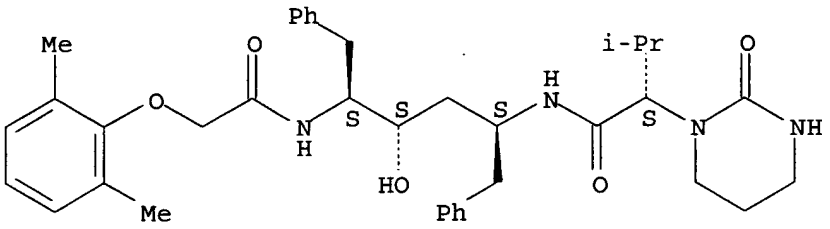
IT **192725-17-0**, ABT-378
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(In vitro metabolism of HIV-1 protease inhibitor ABT-378 in relation to species comparison and metabolite identification in human and laboratory animal liver microsomes)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 210 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:9711 HCAPLUS

DOCUMENT NUMBER: 130:71577

TITLE: Methods of increasing the bioavailability of stable crystal polymorphs of a compound

INVENTOR(S): Chaturvedi, Pravin Ramsewak; Boger, Joshua S.; Tung, Roger Dennis

PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9857648	A1	19981223	WO 1998-US12474	19980616 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9881451	A1	19990104	AU 1998-81451	19980616 <--
PRIORITY APPLN. INFO.:			US 1997-876558 A	19970616
			WO 1998-US12474 W	19980616

AB The present invention relates to methods of increasing the bioavailability of the most stable crystalline form of a compound, i.e. aspartyl protease inhibitor. The invention also relates to particles of the most stable crystalline form of a compound having an average particle size of less than 400 nm.

The invention further relates to pharmaceutical compns. comprising these

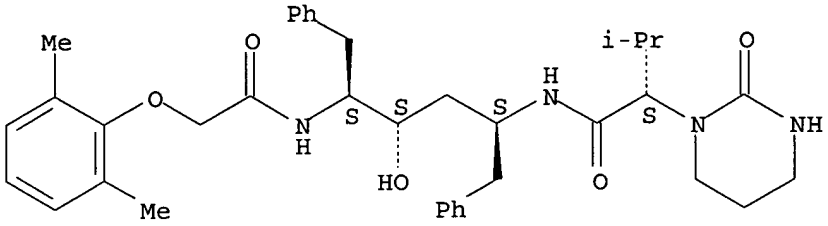
particles and the use of such pharmaceutical compns. for treating diseases, such as HIV. VX-478 polymorph Form V was subjected to wet milling in the presence of hydroxypropyl cellulose and sodium lauryl sulfate to have particles with a mean particle size of 157 nm. The particles were formulated into a suspension, which was administered to rats and pharmacokinetic studies were performed.

IT **192725-17-0**, ABT 378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(particle size reduction of stable crystal polymorphs of aspartyl protease inhibitors to increase bioavailability)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 211 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:708925 HCAPLUS
DOCUMENT NUMBER: 129:347287
TITLE: Nanosized aspartyl protease inhibitors
INVENTOR(S): Chaturvedi, Pravin Ramsewak; Tung, Roger Dennis; Boger, Joshua S.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847492	A1	19981029	WO 1998-US7845	19980414 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9871338	A1	19981113	AU 1998-71338	19980414 <--

PRIORITY APPLN. INFO.: US 1997-844015 A2 19970418
WO 1998-US7845 W 19980414

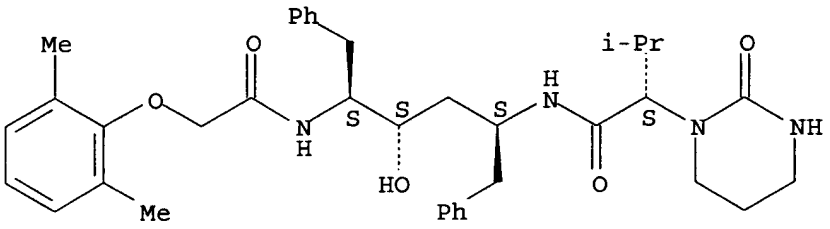
AB The present invention relates to particles of the free base form of aspartyl protease inhibitors and pharmaceutical dosage forms containing those particles. The invention also relates to methods of treating mammals with those pharmaceutical dosage forms.

IT **192725-17-0**, ABT 378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nanoparticle delivery forms for aspartyl protease inhibitors)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 212 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:704756 HCAPLUS
DOCUMENT NUMBER: 130:60638
TITLE: Human serum attenuates the activity of protease inhibitors toward wild-type and mutant human immunodeficiency virus
AUTHOR(S): Molla, Akhteruzzaman; Vasavanonda, Sudthida; Kumar, Gondi; Sham, Hing L.; Johnson, Marianne; Grabowski, Brian; Denissen, Jon F.; Kohlbrenner, William; Plattner, Jacob J.; Leonard, John M.; Norbeck, Daniel W.; Kempf, Dale J.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Virology (**1998**), 250(2), 255-262
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potency of therapeutic regimens containing human immunodeficiency virus (HIV) protease inhibitors is related to the ability to maintain concns. of drug in the plasma of patients that are sufficient for blocking viral replication. The estimation of concns. required for in vivo activity using in vitro assays is complicated by the fact that extensive binding of many protease inhibitors to serum proteins attenuates their antiviral potency. To provide insight into the relative in vivo potency of current protease inhibitors, we assayed their in vitro activity against wild-type and mutant HIV in the presence of human serum (HS). Using this assay,

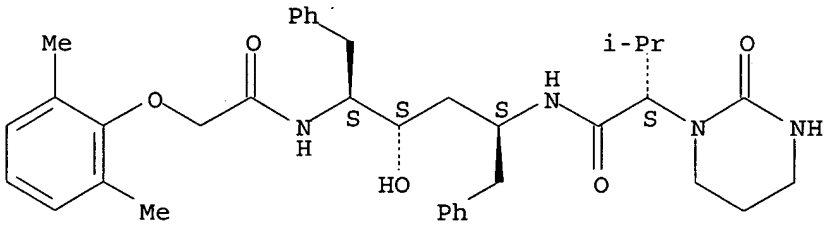
ABT-378, a new protease inhibitor with trough levels in humans far in excess of the EC50 in the presence of 50% HS, was identified. The antiviral activity of ABT-378 was only modestly attenuated by HS, in contrast to ritonavir, saquinavir, and nelfinavir. Examination of the effect of individual serum components suggested that the activity of ABT-378 is affected predominantly by binding to α1-acid glycoprotein (AGP) while the activity of ritonavir is modulated by both AGP and albumin. The method described here may provide insight into the in vivo potency of protease inhibitors and be useful for the preclin. evaluation and selection of new protease inhibitors for clin. studies. (c) 1998 Academic Press.

IT **192725-17-0**, ABT 378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(human serum attenuates the activity of protease inhibitors toward wild-type and mutant HIV virus)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 213 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:540539 HCAPLUS

DOCUMENT NUMBER: 129:254397

TITLE: In vitro selection and characterization of human immunodeficiency virus type 1 variants with increased resistance to ABT-378, a novel protease inhibitor

AUTHOR(S): Carrillo, Alejandro; Stewart, Kent D.; Sham, Hing L.; Norbeck, Daniel W.; Kohlbrenner, William E.; Leonard, John M.; Kempf, Dale J.; Molla, Akhteruzzman

CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA

SOURCE: Journal of Virology (**1998**), 72(9), 7532-7541
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB ABT-378, a new human immunodeficiency virus type 1 (HIV-1) protease inhibitor which is significantly more active than ritonavir in cell culture, is currently under investigation for the treatment of AIDS. Development of viral resistance to ABT-378 in vitro was studied by serial passage of HIV-1 (pNL4-3) in MT-4 cells. Selection of viral variants with increasing concns. of ABT-378 revealed a sequential appearance of

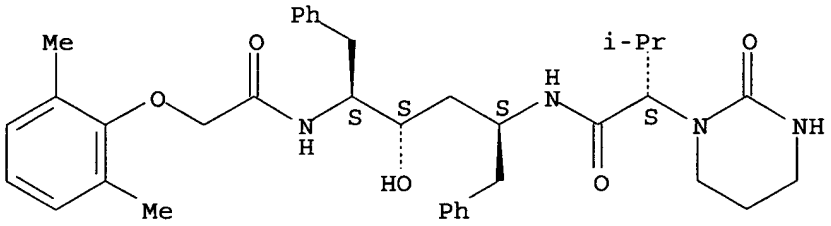
mutations in the protease gene: 184V-L10F-M46I-T91S-V32I-147V. Further selection at a 3.0 μM inhibitor concentration resulted in an addnl. change at residue 47 (V47A), as well as reversion at residue 32 back to the wild-type sequence. The 50% effective concentration of ABT-378 against passaged virus containing these addnl. changes was 338-fold higher than that against wild-type virus. In addition to changes in the protease gene, sequence anal. of passaged virus revealed mutations in the p1/p6 (P1' residue Leu to Phe) and p7/p1 (P2 residue Ala to Val) gag proteolytic processing sites. The p1/p6 mutation appeared in several clones derived from early passages and was present in all clones obtained from passage P11 (0.42 μM ABT-378) onward. The p7/p1 mutation appeared very late during the selection process and was strongly associated with the emergence of the addnl. change at residue 47 (V47A) and the reversion at residue 32 back to the wild-type sequence. Furthermore, this p7/p1 mutation was present in all clones obtained from passage P17 (3.0 μM ABT-378) onward and always occurred in conjunction with the p1/p6 mutation. Full-length mol. clones containing protease mutations observed very late during the selection process were constructed and viable only in the presence of both the p7/p1 and p1/p6 cleavage-site mutations. This suggests that mutation of these gag proteolytic cleavage sites is required for the growth of highly resistant HIV-1 selected by ABT-378 and supports recent work demonstrating that mutations in the p7/p1/p6 region play an important role in conferring resistance to protease inhibitors (L. Doyon et al., J. Virol. 70:3763-3769, 1996; Y. M. Zhang et al., J. Virol. 71:6662-6670, 1997).

IT **192725-17-0**, ABT 378
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ABT 378; in vitro selection and characterization of human immunodeficiency virus type 1 variants with increased resistance to novel protease inhibitor ABT-378 with mutations in protease gene)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 214 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:351758 HCAPLUS
DOCUMENT NUMBER: 129:45325
TITLE: Liquid pharmaceutical compositions containing HIV protease inhibitors
INVENTOR(S): Lipari, John; Al-Razzak, Laman A.; Ghosh, Soumojeet;

Gao, Rong; Kaul, Dilip
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822106	A1	19980528	WO 1997-US20794	19971112 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9710071	A	19980525	ZA 1997-10071	19971107 <--
CA 2271196	AA	19980528	CA 1997-2271196	19971112 <--
CA 2271196	C	19980528		
CA 2505430	AA	19980528	CA 1997-2505430	19971112 <--
AU 9852573	A1	19980610	AU 1998-52573	19971112 <--
AU 717546	B2	20000330		
EP 942721	A1	19990922	EP 1997-947510	19971112 <--
EP 942721	B1	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
CN 1248914	A	20000329	CN 1997-199780	19971112 <--
BR 9714310	A	20000502	BR 1997-14310	19971112 <--
JP 2000515555	T2	20001121	JP 1998-523751	19971112 <--
JP 3592337	B2	20041124		
TR 9901129	T2	20010521	TR 1999-9901129	19971112 <--
NZ 335002	A	20010831	NZ 1997-335002	19971112 <--
EP 1283041	A1	20030212	EP 2002-11533	19971112 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
AT 231393	E	20030215	AT 1997-947510	19971112 <--
PT 942721	T	20030630	PT 1997-947510	19971112 <--
IL 129300	A1	20030706	IL 1997-129300	19971112 <--
ES 2191862	T3	20030916	ES 1997-947510	19971112 <--
TW 475895	B	20020211	TW 1997-86117136	19971117 <--
NO 9902427	A	19990720	NO 1999-2427	19990520 <--
KR 2000057169	A	20000915	KR 1999-704469	19990520 <--
BG 64411	B1	20050131	BG 1999-103425	19990521
HK 1022441	A1	20031031	HK 2000-101651	20000317 <--
AU 757970	B2	20030313	AU 2000-39414	20000609 <--
JP 2004346077	A2	20041209	JP 2004-163024	20040601

PRIORITY APPLN. INFO.:		
US 1996-754390	A	19961121
AU 1998-52573	A3	19971112
CA 1997-2271196	A3	19971112
EP 1997-947510	A3	19971112
JP 1998-523751	A3	19971112
WO 1997-US20794	W	19971112

AB A liquid pharmaceutical composition providing improved oral bioavailability is disclosed for compds. which are inhibitors of HIV protease. In particular, the composition comprises a solution in a pharmaceutically acceptable

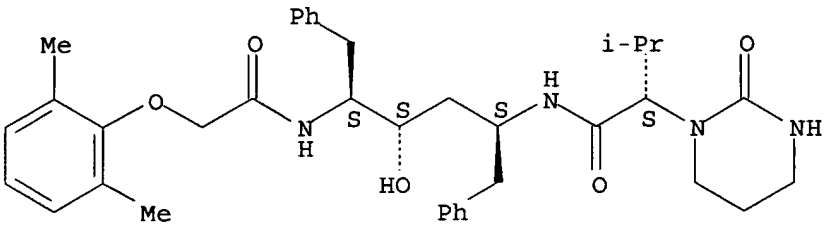
organic solvent of (a) the HIV protease inhibitor and optionally, (b) a surfactant. The composition can optionally be encapsulated in either hard gelating capsules or soft elastic capsules (SEC). A capsule composition was prepared containing ritonavir 20, ethanol 10, oleic acid 69.99, and BHT 0.01% by weight

IT **192725-17-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liquid pharmaceutical compns. containing HIV protease inhibitors)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

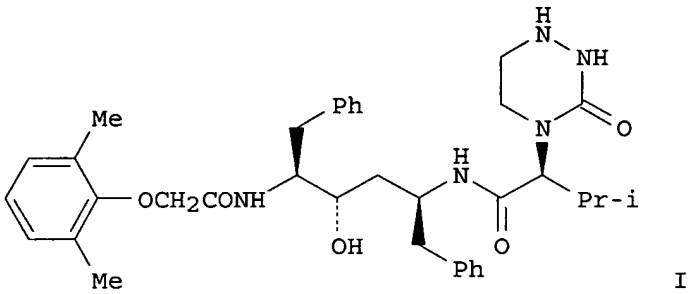
L15 ANSWER 215 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:515728 HCAPLUS
DOCUMENT NUMBER: 127:122001
TITLE: Preparation of peptide analogs as retroviral protease inhibitors
INVENTOR(S): Sham, Hing Leung; Norbeck, Daniel W.; Chen, Xiaoqi; Betebenner, David A.; Kempf, Dale J.; Herrin, Thomas R.; Kumar, Gondi N.; Condon, Stephen L.; Cooper, Arthur J.; Dickman, Daniel A.; Hannick, Steven M.; Kolaczkowski, Lawrence; Oliver, Patricia A.; Plata, Daniel J.; Stengel, Peter J.; Stoner, Eric J.; Tien, Jieh-Heh J.; Liu, Jih-Hua; Patel, Ketan M.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721685	A1	19970619	WO 1996-US20440	19961206 <--
W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NZ				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5914332	A	19990622	US 1996-753201	19961121 <--
AU 9713422	A1	19970703	AU 1997-13422	19961206 <--
AU 725369	B2	20001012		
EP 882024	A1	19981209	EP 1996-944941	19961206 <--

EP 882024	B1	20020206				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI						
JP 2000502085	T2	20000222	JP 1997-522278		19961206	<--
JP 3170292	B2	20010528				
AT 212986	E	20020215	AT 1996-944941		19961206	<--
EP 1295874	A2	20030326	EP 2002-26856		19961206	<--
EP 1295874	A3	20030402				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI						
HK 1016585	A1	20020809	HK 1999-101462		19990409	<--
PRIORITY APPLN. INFO.:			US 1995-572226	A	19951213	
			US 1996-753201	A	19961121	
			US 1996-754687	A	19961121	
			EP 1996-943605	A3	19961206	
			WO 1996-US20440	W	19961206	

OTHER SOURCE(S): MARPAT 127:122001

GI



I

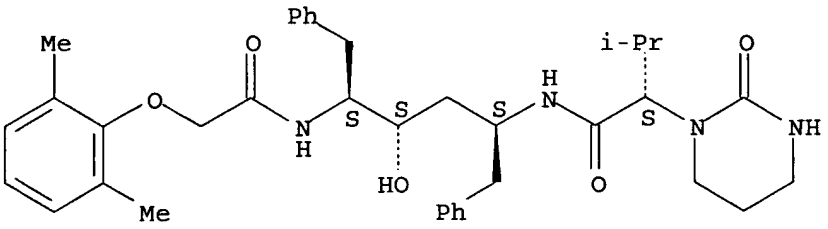
AB R4 -L1-CONHCHR1CH(OH)CH2CHR2NHCOCHR3R5 [R1, R2 = lower alkyl, cycloalkylalkyl, arylalkyl; R3 = lower alkyl, hydroxyalkyl, cycloalkylalkyl; R4 = aryl, heterocyclyl; R5 = heterocyclyl e.g. Q - Q4; wherein m, n = 1-3; p = 1,2; X = O, S, NH; Y = CH2, O, S, (un)substituted NH; Z = O, S, NH; L1 = O, S, (un)substituted NH, O-alkylenyl, S(O)m-alkylenyl (wherein m = 0, 1,2), N-(un)substituted NH-alkylenyl, alkylenyl, alkenylenyl, etc.] are prepared Methods and compns. for inhibiting an HIV infection are also disclosed. Thus, (2S)-(4-benzyloxycarbonylaza-1-tetrahydropyrimid-2-onyl)-3-methylbutanoic acid (preparation given) was condensed with (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-amino-1,6-diphenylhexane using standard coupling procedure [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/DMF] followed by hydrogenolysis over 10% Pd-C to give the title compound (I). I in vitro at 0.5 nmol inhibited HIV protease by 94.6%.

IT **192725-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide analogs as retroviral protease inhibitors for inhibiting HIV infection)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

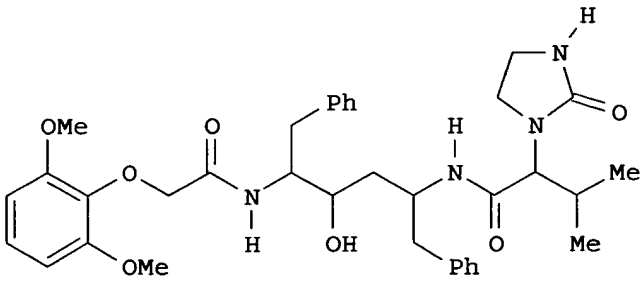


L15 ANSWER 216 OF 216 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:515727 HCAPLUS
DOCUMENT NUMBER: 127:121994
TITLE: Preparation and formulation of N-(α-aminoacyl)diaminohydroxyalkanes as HIV protease inhibitors
INVENTOR(S): Sham, Hing Leung; Stewart, Kent D.; Kempf, Dale J.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721683	A1	19970619	WO 1996-US19394	19961206 <--
W: CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2238977	AA	19970619	CA 1996-2238977	19961206 <--
EP 876353	A1	19981111	EP 1996-943605	19961206 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000502997	T2	20000314	JP 1997-522112	19961206 <--
EP 1295874	A2	20030326	EP 2002-26856	19961206 <--
EP 1295874	A3	20030402		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

PRIORITY APPLN. INFO.:
US 1995-572226 A 19951213
US 1996-754687 A 19961121
EP 1996-943605 A3 19961206
WO 1996-US19394 W 19961206

OTHER SOURCE(S): MARPAT 127:121994
GI



I

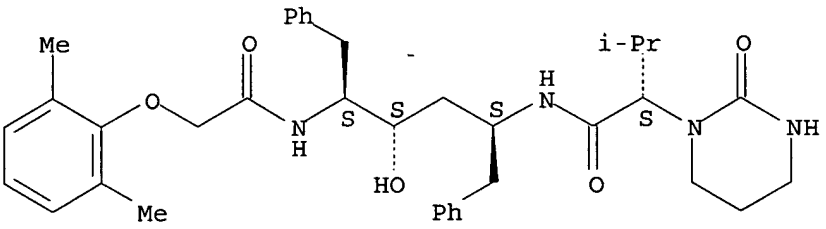
AB R4ZCONHCHR1CH(OH)CH2CHR2NHCOCHR3R5 [I; R1,R2 = (cyclo)alkyl, aralkyl; R3 = (cyclo)alkyl, hydroxyalkyl; R4 = heterocyclyl or aryl; R5 = N-attached oxoheterocyclyl, etc.] were prepared Thus, (S)-(PhCH2)2NCH(CH2Ph)COCH2CN (preparation given) was condensed with PhCH2MgCl and the product reduced by NaBH4 to give (S,S,S)-(PhCH2)2NCH(CH2Ph)CH(OH)CH2CH(NH2)CH2Ph. The latter was N-protected and the N-debenzylated product amidated by 2,6-(MeO)C6H3OCH2CO2H (preparation given) to give, after deprotection and amidation by (S)-Me2CHCHR5CO2H (R5 = 2-oxo-1H-imidazol-3-yl)(preparation given), title compound (S,S,S,S)-II. Data for biol. activity of I were given.

IT **192725-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and formulation of N-(α-aminoacyl)diaminohydroxyalkanes as HIV protease inhibitors)

RN 192725-17-0 HCAPLUS

CN 1(2H)-Pyrimidineacetamide, N-[(1S,3S,4S)-4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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=> d que stat l19
L16             QUE  ABB=ON  PLU=ON  LOPINAVIR?(P)(ANTIBOD? OR ANTIGEN? O
                R HAPTEN? OR LABEL? OR TRACE? OR BIOTIN? OR IMMUNO? OR AV
                IDIN? OR STREPTAVID? OR BSA OR BOVINE? OR KLH OR KEYHOLE?
                 OR BTG OR OVA OR OVALBUM? OR NHS OR N-HYDROXYSUCC?)
L17         506 SEA L16
L18         288 DUP REM L17 (218 DUPLICATES REMOVED)
L19          93 SEA L18 AND PY<2004
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=> d l19 ibib ab hitind 1-93

L19 ANSWER 1 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259527 HCAPLUS
DOCUMENT NUMBER: 142:329801
TITLE: Atazanavir conjugates and antibodies useful in immunoassay
INVENTOR(S): Root, Richard T.; Hui, Raymond A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 669,831.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 2005064517	A1	20050324	US 2004-982611		20041105	
US 2003100088	A1	20030529	US 2002-192052		20020710	<--
US 2004127689	A1	20040701	US 2003-669831		20030924	
PRIORITY APPLN. INFO.:			US 2001-305192P	P	20010713	
			~~US 2002-192052~~	A2	20020710	
			US 2003-669831	A2	20030924	

OTHER SOURCE(S): MARPAT 142:329801
AB The invention discloses activated haptens useful for generating immunogens to the HIV protease inhibitor atazanavir, immunogens useful for producing antibodies to atazanavir, and antibodies and labeled conjugates useful in immunoassays for determination of atazanavir. The haptens feature an activated functionality at the central, non-terminal hydroxyl group.
IC ICM G01N033-53
ICS C07D473-14
INCL 435007100; 514263200; 544269000; 534551000; 530409000
CC 1-1 (Pharmacology)
Section cross-reference(s): 15
IT 4385-62-0, 4-Pyridin-2-ylbenzoic acid 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (cross-reactivity; atazanavir conjugates and **antibodies** useful in **immunoassay**)

L19 ANSWER 2 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:534032 HCAPLUS
DOCUMENT NUMBER: 141:70254
TITLE: Monoclonal antibodies specific to haptens comprising protease inhibitor conjugates for immunoassay
INVENTOR(S): Sigler, Gerald F.; Hui, Raymond A.; Deras, Ina; Root, Richard Terry; Ghoshal, Mitali; Huber, Erasmus; Von Der Eltz, Herbert W.; Metz, Sigrun; Kern, Peter
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 52 pp., Cont.-in-part of U.S. Ser. No. 192,052.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004127689	A1	20040701	US 2003-669831	20030924
US 2003100088	A1	20030529	US 2002-192052	20020710 <--
CA 2482232	AA	20050324	CA 2004-2482232	20040920
EP 1519192	A2	20050330	EP 2004-22393	20040921
EP 1519192	A3	20050608		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2005097307	A2	20050414	JP 2004-277754	20040924
US 2005064517	A1	20050324	US 2004-982611	20041105
US 2005148596	A1	20050707	US 2004-988477	20041112

PRIORITY APPLN. INFO.: US 2001-305192P P 20010713
US 2002-192052 A2 20020710
US 2003-669831 A 20030924

OTHER SOURCE(S): MARPAT 141:70254

AB Activated **haptens** useful for generating **immunogens** to HIV protease inhibitors, **immunogens** useful for producing **antibodies** to HIV protease inhibitors, and **antibodies** and **labeled** conjugates useful in **immunoassays** for and monitoring therapeutic HIV protease inhibitors. The novel **haptens** feature an activated functionality at the central, non-terminal hydroxyl group common to all HIV protease inhibitors, e.g., saquinavir, nelfinavir, indinavir, amprenavir, ritonavir, **lopinavir**, and atazanavir.

IC ICM C07K014-16
ICS C12Q001-70; A61K031-551; C07D487-14

INCL 530395000; 534560000; 540495000; 435005000

CC 15-3 (Immunochemistry)
Section cross-reference(s): 1, 9

IT 127779-20-8DP, Saquinavir, conjugates 149845-06-7P 150378-17-9P, Indinavir 155213-67-5DP, Ritonavir, conjugates 157810-81-6P, Indinavir sulfate 159989-64-7P, Nelfinavir 161814-49-9P, Amprenavir 192725-17-0P, **Lopinavir** 198904-31-3P, Atazanavir
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(monoclonal **antibodies** specific to **haptens** comprising protease inhibitor conjugates for **immunoassay**)

L19 ANSWER 3 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:186162 HCAPLUS
DOCUMENT NUMBER: 140:228554
TITLE: No influence of the P-glycoprotein genotype (MDR1 C3435T) on plasma levels of lopinavir and efavirenz during antiretroviral treatment
AUTHOR(S): Winzer, R.; Langmann, P.; Zilly, M.; Tollmann, F.; Schubert, J.; Klinker, H.; Weissbrich, B.
CORPORATE SOURCE: Medical Policlinic, Division of Infectious Diseases, University of Wuerzburg, Germany
SOURCE: European Journal of Medical Research (**2003**), 8(12), 531-534
CODEN: EJMRFL; ISSN: 0949-2321
PUBLISHER: I. Holzapfel Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: In a retrospective study of HIV patients under antiretroviral therapy, the authors investigated the influence of the MDR1 genotype (C3435T) on plasma levels of lopinavir (LPV) and efavirenz (EFV). Methods: The MDR1 genotype was analyzed from 67 patients who were treated with LPV (n = 32; mean treatment period 53 wk) and/or EFV (n = 43, mean treatment period 105 wk) between 1999 and 2003. Plasma levels of LPV (trough levels) and EFV (12-h-levels) were determined every three months. Data were analyzed by the Kruskal-Wallis test. Results: There were no significant differences in the LPV and EFV plasma levels with respect to the MDR1 3435 genotype. Conclusions: The authors did not find evidence for an influence of the MDR1 3435 genotype on plasma levels of LPV and EFV.

CC 1-5 (Pharmacology)

IT AIDS (disease)
Anti-AIDS agents
Genetic polymorphism
Genotypes
Human
Human **immunodeficiency** virus 1
(no influence of P-glycoprotein genotype (MDR1 C3435T) on plasma levels of **lopinavir** and efavirenz during antiretroviral treatment)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:165851 HCAPLUS
DOCUMENT NUMBER: 140:245891
TITLE: Hepatotoxicity associated with antiretroviral therapy containing HIV-1 protease inhibitors
AUTHOR(S): Sulkowski, Mark S.
CORPORATE SOURCE: Johns Hopkins Medical Institutions, Baltimore, MD, USA
SOURCE: Seminars in Liver Disease (**2003**), 23(2), 183-193
CODEN: SLDIEE; ISSN: 0272-8087
PUBLISHER: Thieme Medical Publishers, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Human **immunodeficiency** virus 1 (HIV-1) protease inhibitors are important components of highly active antiretroviral therapy and have had a profound impact on the natural history of HIV and AIDS. However, in the era of highly active antiretroviral therapy (HAART), drug-induced hepatotoxicity or liver injury has emerged as an important potential complication of combination antiretroviral therapy, particularly those regimens containing protease inhibitors (PIs). Liver injury has been associated with each of the six PIs currently approved by the U.S. Food and Drug Administration (FDA), most commonly with administration of full dose ritonavir (600 mg bid or 400 mg bid with saquinavir). However, this regimen has been largely replaced by the use of low-dose ritonavir (≤ 200 mg bid) to pharmacol. "boost" other PI, such as **lopinavir** or indinavir, which has not been associated with an increased risk of hepatotoxicity compared with other PIs. Coinfection with hepatitis C virus (HCV) and B virus (HBV) remains an important risk factor for the development of HAART-associated liver injury. Although studies indicate that coinfected patients can be safely treated with PIs, such patients should be closely monitored. In addition, although unsubstantiated, some experts recommend evaluation or treatment, or both, of underlying chronic viral hepatitis prior to the initiation of antiretroviral therapy. Further research is needed to understand the etiopathogenesis of PI-associated liver injury, particularly among patients

with hepatitis B or C infection.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:135163 HCAPLUS
TITLE: The effects of highly antiretroviral therapy on triglyceride and cholesterol levels in patients with HIV/AIDS
AUTHOR(S): Grate, Elizabeth; Simpson, Kit
CORPORATE SOURCE: Claflin Univ., Orangeburg, SC, USA
SOURCE: Abstracts, 55th Southeast Regional Meeting of the American Chemical Society, Atlanta, GA, United States, November 16-19, 2003 (**2003**), 917. American Chemical Society: Washington, D. C.
CODEN: 69EUCH
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Background: The current treatment regimen for human **immunodeficiency** virus (HIV) is referred to as highly active antiretroviral therapy (HAART). This treatment regimen consists of antiviral medications from three different classes: (1) nucleoside reverse transcriptase inhibitors, (2) non-nucleoside reverse transcriptase inhibitors and (3) protease inhibitors. The purpose of this combination is to slow the progression of HIV to AIDS by significantly lowering or maintaining the viral load. Specifically, the protease inhibitors have been noted to cause a significant risk in both triglyceride and cholesterol levels. A popular protease inhibitor combination, Kaletra (ritonavir and **lopinavir**), has produced significant redns. in viral loads as a component of HAART at the expense of large increases in blood lipid levels. However, Reyataz (atazanavir) is a new protease inhibitor that has shown that it is equally effective to its drug counterparts without the disruption in lipid levels. Objective: Quantify the association between two specific antiviral agents, (Kaletra and Reyataz) and its effects on triglyceride and cholesterol level. Methods: A literature search was conducted to address this area of this study. Literature databases that were utilized included: Current Contents, Medline, PubMed and various Internet resources. Articles reviewed included, but were not limited to, prospective and cohort studies involving primary data dealing with human subjects in the English language and also, studies involving elevated triglycerides and cholesterol levels associated with HAART. An anal. was conducted on the association involving protease inhibitors, triglycerides, and total cholesterol. Results: Antiretroviral drugs, especially protease inhibitors, have been associated with a moderate rise in the triglycerides (1.1 mmol/L) and cholesterol (0.73mmol/L) levels in patients with HIV/AIDS. involving HAART therapy (specifically protease inhibitors) and elevated triglycerides and cholesterol as components of the metabolic syndrome. The increase in triglyceride and cholesterol levels may vary from patient to patient, but in some cases may be quite extreme and lead to serious complications. Conclusion: Currently, there is growing evidence ture research could include modeling the expected differences in quality-adjusted survival and cost among the two treatment groups.

L19 ANSWER 6 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:12297 HCAPLUS
DOCUMENT NUMBER: 140:52845

TITLE: Immune reconstitution is comparable in antiretroviral-naive subjects after 1 year of successful therapy with a nucleoside reverse-transcriptase inhibitor- or protease inhibitor-containing antiretroviral regimen
AUTHOR(S): Landay, Alan L.; Spritzler, John; Kessler, Harold; Mildvan, Donna; Pu, Minya; Fox, Larry; O'Neil, Dorothy; Schock, Barbara; Kuritzkes, Daniel; Lederman, Michael M.
CORPORATE SOURCE: AIDS Clinical Trials Group 5014 Team, Departments of Immunology/Microbiology and Medicine, Rush Medical College, Chicago, IL, USA
SOURCE: Journal of Infectious Diseases (**2003**), 188(10), 1444-1454
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We compared immune restoration in patients who suppressed human immunodeficiency virus type 1 replication after treatment with a protease inhibitor (PI) plus nevirapine or with 3 nucleoside reverse-transcriptase inhibitors (NRTIs) plus nevirapine. Changes in total and memory CD4 and CD8 cells were similar in the groups, as were decreases in immune activation (e.g., CD38 and HLA-DR) and increases in CD28 expression. Increases in naive CD4 and CD8 cells tended to be greater in the NRTI-treated group, with differences in naive CD4 cells significant at weeks 8 and 12 ($P<.05$) but not at week 48. Lymphocyte apoptosis decreased in both groups, but the week-1 decrease was greater in the PI-treated group ($P< .02$). Lymphocyte proliferation and skin-test responses were comparable. We find little evidence for differences in the major direct immunol. effect of PI vs. NRTI regimens and propose that effects observed elsewhere were indirect, mediated through antiviral activity or adaptation of the virus to selection pressure.
CC 1-5 (Pharmacology)
IT 3056-17-5, Stavudine 129618-40-2, Nevirapine 134678-17-4, Lamivudine 136470-78-5, Abacavir 155213-67-5, Ritonavir 192725-17-0, **Lopinavir**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**immunol**. effect of nucleoside reverse-transcriptase inhibitor vs. protease inhibitor-containing antiretroviral regimen in patients with HIV)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:994234 HCAPLUS
DOCUMENT NUMBER: 140:12392
TITLE: New patterns of HIV-1 resistance during HAART
AUTHOR(S): Fumero, E.; Podzamczer, D.
CORPORATE SOURCE: Infectious Disease Service, Hospital Universitari de Bellvitge, Barcelona, Spain
SOURCE: Clinical Microbiology and Infection (**2003**), 9(11), 1077-1084
CODEN: CMINFM; ISSN: 1198-743X
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. HIV-1 resistance and subsequent virol. failure occur in a

substantial proportion of HIV-infected patients receiving HAART regimens. In the present article, we summarize new data on resistance to current and forthcoming antiretroviral drugs which will help in the interpretation of the results of resistance tests and the individualization of therapy. Nucleoside analog mutations (NAMs) (M41L, D67N, K70R, L210W, T215Y/F and K219Q/E) are associated with reduced susceptibility to most nucleoside analogs and the nucleotide tenofovir. This recently approved drug has shown a reduced virol. response in the presence of three or more NAMs, including M41L or L210W, as well as in the presence of T69 insertions. Hypersusceptibility (IC50 < 0.5) to non-nucleoside reverse transcriptase inhibitors (NNRTIs) has recently been described in association with increased resistance to nucleoside analogs, and it seems to enhance the **immunol**. and virol. responses in patients receiving efavirenz-containing regimens. New protease inhibitors (PIs) have a lower cross-resistance profile, although more clin. data are needed to establish appropriate PI sequencing to promote sustained virol. success. Cross-resistance between amprenavir (APV) and **lopinavir** (LPV/r) in the presence of only four APV-related mutations has been described, suggesting that phenotypic tests should be applied before prescribing LPV/r to APV-experienced patients. Resistance to the new entry inhibitor class compound T-20 (enfuvirtide) has also been detected.

CC 1-0 (Pharmacology)

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 8 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:947388 HCAPLUS

DOCUMENT NUMBER: 139:390786

TITLE: Interleukin-7 levels may predict virological response in advanced HIV-1-infected patients receiving lopinavir/ritonavir-based therapy

AUTHOR(S): Boulassel, M. R.; Smith, G. H. R.; Gilmore, N.; Klein, M.; Murphy, T.; MacLeod, J.; LeBlanc, R.; Allan, J.; Rene, P.; Lalonde, R. G.; Routy, J. P.

CORPORATE SOURCE: Immunodeficiency Service, McGill University Health Centre, Montreal, QC, Can.

SOURCE: HIV Medicine (**2003**), 4(4), 315-320
CODEN: HMIEAB; ISSN: 1464-2662

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objectives: To examine the relationship between levels of the T-cell regulatory cytokine interleukin-7 (IL-7) and CD4 cell counts during immune reconstitution and to assess its prognostic value in advanced HIV-1-infected patients receiving **lopinavir**/ritonavir-based therapy. Methods: Thirty-six HIV-1-infected adults who completed 48 wk of follow-up visits were included in this prospective study. Patients having failed two or more antiretroviral therapy regimens were treated with **lopinavir**/ritonavir-based therapy. An ELISA was used to determine IL-7 plasma levels, flow cytometry was used to analyze cell surface **antigens**, and polymerase chain reaction was used to quantify plasma HIV-1. Results: Pretreatment IL-7 levels were elevated in all patients (mean 11.0 pg/mL) and were neg. correlated with CD4 cell counts and age ($r = -0.59$, $P < 0.001$ and $r = -0.57$, $P < 0.001$, resp.). During the course of treatment, IL-7 levels decreased by 34% while CD4 cell nos. progressively increased by 88%. Multivariate regression anal. showed that only pretreatment IL-7 levels predicted viral load at 48 wk when controlling for baseline CD4 cell counts, viral load and patient demographics. Conclusions: These findings are consistent with regulation

of T-cell recovery by IL-7, and suggest that IL-7 measurements might be used to predict virol. response.
CC 1-5 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
Biomarkers
CD4-positive T cell
CD8-positive T cell
Human
Human **immunodeficiency** virus 1
(interleukin-7 levels may predict virol. response in advanced HIV-1-infected patients receiving **lopinavir**/ritonavir-based therapy)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:901779 HCAPLUS
DOCUMENT NUMBER: 140:228523
TITLE: Therapeutic drug monitoring of the HIV/AIDS drugs abacavir, zidovudine, efavirenz, nevirapine, indinavir, lopinavir, and nelfinavir
AUTHOR(S): Donnerer, J.; Kronawetter, M.; Kapper, A.; Haas, I.; Kessler, H. H.
CORPORATE SOURCE: Institute of Experimental and Clinical Pharmacology, Karl Franzens University, Graz, Austria
SOURCE: Pharmacology (**2003**), 69(4), 197-204
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Combination therapy with antiretroviral drugs is used for the treatment of patients infected with the human **immunodeficiency** virus. To achieve optimal drug concns. for viral suppression and avoidance of drug toxicity, monitoring of drug levels has been considered essential. We set up an anal. procedure for monitoring the plasma concns. of a total of seven drugs: abacavir, zidovudine, efavirenz, nevirapine, indinavir, **lopinavir**, and nelfinavir. The plasma samples were liquid/liquid extracted and subjected to high-performance liquid chromatog. (HPLC) anal. The compds. were monitored by UV detection: indinavir, **lopinavir**, and nelfinavir at 215 nm; efavirenz at 254 nm, and abacavir, zidovudine, and nevirapine at 266 nm. Two different extraction procedures and two different HPLC eluents on a C8 reversed-phase HPLC column were used to monitor all seven compds. Under steady state conditions, the plasma concns. of antiviral drugs in 175 patients were correlated with the time after the last dosing to define the peak or trough levels. Due to the short plasma elimination half-life of abacavir and zidovudine, only peak levels could be determined for these compds., whereas both peak and trough levels could be assessed for the other compds. because of a longer plasma elimination half-life. The mean peak concns. (μg/mL) were 0.69 for abacavir and 0.57 for zidovudine; the mean peak/trough concns. (μg/mL) were 2.07/1.32 for efavirenz, 2.43/2.23 for nevirapine, 5.48/1.08 for indinavir, 4.69/3.51 for **lopinavir**, and 3.54/1.45 for nelfinavir. The described anal. method offers a broad-spectrum monitoring of plasma levels of antiretroviral drugs.
CC 1-5 (Pharmacology)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 10 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:891262 HCAPLUS
DOCUMENT NUMBER: 139:374074
TITLE: The role of lopinavir/ritonavir (Kaletra) in the management of HIV infected adults
AUTHOR(S): Walmsley, Sharon; Christian, Michael D.
CORPORATE SOURCE: University of Toronto, Toronto, ON, M5G 2C4, Can.
SOURCE: Expert Review of Anti-Infective Therapy (**2003**), 1(3), 389-401
CODEN: ERATCK; ISSN: 1478-7210
PUBLISHER: Future Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. As the HIV pandemic enters its third decade, more sophisticated and efficacious therapies are continually being developed. This article provides an in-depth review of the first coformulated boosted protease inhibitor available on the world market, lopinavir/ritonavir (Kaletra). Included in this review is an overview of the current market place, the chemical, pharmacokinetics, clin. efficacy and side-effect profile or lopinavir/ritonavir. In addition, an expert opinion and commentary on the clin. applications of this drug is provided.
CC 1-0 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(role of **lopinavir**/ritonavir (Kaletra) in the management of HIV infected adults)
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 11 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:860238 HCAPLUS
DOCUMENT NUMBER: 140:192059
TITLE: Simultaneous determination of six HIV protease inhibitors, one metabolite, and two non-nucleoside reverse transcriptase inhibitors in human plasma by isocratic reversed-phase liquid chromatography after solid-phase extraction
AUTHOR(S): Faux, J.; Venisse, N.; Le Moal, G.; Dupuis, A.; Bouguet, S.
CORPORATE SOURCE: Laboratoire de Pharmacocinetique, C.H.U de Poitiers, Poitiers, 86021, Fr.
SOURCE: Chromatographia (**2003**), 58(7/8), 421-426
CODEN: CHRGB7; ISSN: 0009-5893
PUBLISHER: Friedrich Vieweg & Sohn Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A selective and sensitive HPLC method was developed and validated for the determination of six human **immunodeficiency** virus (HIV)-protease inhibitors (amprenavir, indinavir, **lopinavir**, nelfinavir, ritonavir, and saquinavir) and two nonnucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) in a single run. This involve a simple liquid-solid extraction on OASIS HLB column in the presence of an internal standard (prazepam). Separation is achieved on a Xterra, C18 (150 + 3.9 mm I. D.) column with a mobile phase consisting of MeCN and 3-(cyclohexylamino)-1-propanesulfonic acid (CAPS) buffer pH 10.5, (37: 63, volume/volume) delivered isocratically. A sequential UV detection (5 min

sequence set at 320 nm for nevirapine acquisition and 55 min at 210 nm for other drugs and internal standard) was performed. The method is linear over the specific ranges studied. Precision and accuracy at four concns. are resp. <13.6% and 9.1% for intraday assays and <4.2% and 5.9% for interday assays. This method is suitable for therapeutic drug monitoring purpose and routinely used in the authors' laboratory
CC 1-1 (Pharmacology)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 12 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:831879 HCAPLUS
DOCUMENT NUMBER: 140:399366
TITLE: Ketoconazole and lopinavir/ritonavir coadministration: Boosting beyond boosting
AUTHOR(S): Boffito, Marta; Bonora, Stefano; Hoggard, Patrick G.; Di Perri, Giovanni
CORPORATE SOURCE: Department of Infectious Diseases, University of Torino, Turin, Italy
SOURCE: AIDS Research and Human Retroviruses (**2003**), 19(10), 941-942
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Coadministration of low-dose ritonavir, as a booster agent, has been successfully adopted as a strategy to improve the pharmacokinetic profile of protease inhibitors, which undergo metabolism by cytochrome P 450 in the gastrointestinal tract and liver. Since both higher drug concns. and reduced frequency of dosing are achieved with ritonavir coadministration, this has become the standard of care in the therapeutic management of HIV-infected subjects. In the setting of cytochrome P 450-based drug-drug interactions, systemic antifungal agents, especially ketoconazole, have been shown to bring about clin. relevant consequences. Coadministration of ketoconazole and ritonavir was found to provide an addnl. increase of lopinavir plasma concns. in a patient with acute HIV infection.
CC 1-4 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
Blood analysis
Drug metabolism
Fungicides
Human
Human **immunodeficiency** virus 1
(pharmacokinetic interaction of ketoconazole and **lopinavir** /ritonavir coadministration)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 13 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:763100 HCAPLUS
DOCUMENT NUMBER: 139:316635
TITLE: The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients
AUTHOR(S): McCance-Katz, Elinore F.; Rainey, Petrie M.; Friedland, Gerald; Jatlow, Peter
CORPORATE SOURCE: Medical College of Virginia, Virginia Commonwealth University, Richmond, USA
SOURCE: Clinical Infectious Diseases (**2003**), 37(4),

476-482
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study examines the pharmacokinetic/pharmacodynamic interactions between (1) lopinavir-ritonavir (L/R), a fixed combination of protease inhibitors used for the treatment of HIV disease, and (2) ritonavir alone at the same dosage as that in the L/R formulation, with methadone, an opiate frequently used in substance abuse pharmacotherapy for opioid (heroin)-dependent injection drug users, many of whom are infected with HIV. L/R was associated with significant redns. in the methadone area under the concentration-time curve (P <.001), maximum concentration (P <.001), and min. concentration (P <.001), as well as increased methadone oral clearance (P <.001) and increased opiate withdrawal symptoms (P =.013), whereas ritonavir use alone modestly and nonsignificantly increased methadone concns. Lopinavir is a potent inducer of methadone metabolism, and treatment with L/R requires clin. monitoring and increased methadone doses in some patients, whereas ritonavir has no significant effect on methadone metabolism
CC 1-4 (Pharmacology)
IT Anti-AIDS agents
Drug withdrawal
Human
Human **immunodeficiency** virus 1
(pharmacokinetic and pharmacodynamic interactions and opioid withdrawal symptoms in patients receiving methadone and **lopinavir** -ritonavir)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 14 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:726089 HCAPLUS
DOCUMENT NUMBER: 140:245677
TITLE: Differentiation of genotypic resistance profiles for amprenavir and lopinavir, a valuable aid for choice of therapy in protease inhibitor-experienced HIV-1-infected subjects
AUTHOR(S): Paulsen, Denise; Elston, Robert; Snowden, Wendy; Tisdale, Margaret; Ross, Lisa
CORPORATE SOURCE: Department of International Clinical Virology, GlaxoSmithKline Inc., Research Triange Park, NC, 27709, USA
SOURCE: Journal of Antimicrobial Chemotherapy (**2003**), 52(3), 319-323
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review on the similarities and differences between the genotypic resistance profiles for amprenavir and lopinavir. While phenotypic data are valuable for understanding resistance, HIV-1 genotyping is critical in making the optimal choice between these two drugs in protease inhibitor-experienced subjects.
CC 1-0 (Pharmacology)
Section cross-reference(s): 3, 10
IT AIDS (disease)
Anti-AIDS agents
Genotypes

Human
Human **immunodeficiency** virus 1
(differentiation of genotypic resistance profiles for amprenavir and **lopinavir**, a valuable aid for choice of therapy in protease inhibitor-experienced HIV-1-infected subjects)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 15 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:719710 HCAPLUS
DOCUMENT NUMBER: 139:244685
TITLE: Nonpeptide immunologic tracer precursors comprising a tyrosyl-(X)n-lysine or lysyl-(X)n-tyrosine motif, method for preparing them, and uses thereof in immunoassays
INVENTOR(S): Cupo, Anny; Le Saint, Cecile; Vincent, Jean-Pierre
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique -CNRS-, Fr.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
~~WO 2003075010~~	A2	20030912	WO 2003-FR707	20030305 <--
WO 2003075010	A3	20040506		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2836996	A1	20030912	FR 2002-2783	20020305 <--
AU 2003227812	A1	20030916	AU 2003-227812	20030305 <--

PRIORITY APPLN. INFO.: FR 2002-2783 A 20020305
WO 2003-FR707 W 20030305

OTHER SOURCE(S): MARPAT 139:244685
AB The invention discloses an immunol. tracer which comprises a nonpeptide hapten coupled with a Tyr-(X)n-Lys or Lys-(X)n-Tyr motif [X = single bond, amino acid (except for lysine, glutamine, asparagine, Tyrosine), succinyl, citrate, hydroxymethyl group,CH2, O, S, CH2O, CHNH; n = 1-20, preferably 1-10, more preferably 1-2]. The invention also discloses methods for preparing the precursors, as well as their use for preparing immunol. markers useful in competitive immunol. assays.
IC ICM G01N033-532
CC 15-1 (Immunochemistry)
Section cross-reference(s): 1, 9
IT 50-36-2, Cocaine 50-44-2, 6-MP 50-89-5, Thymidine, analysis 50-91-9, FdUrd 51-21-8, 5-Fluorouracil 53-79-2, Puromycin 57-27-2, Morphine, analysis 58-61-7, Adenosine, analysis 58-63-9, Inosine 58-96-8, Uridine 65-46-3, Cytidine 69-33-0, Tubercidine 73-03-0, Cordycepine 118-00-3, Guanosine, analysis 147-94-4, Cytosine-β-D-arabinoside

561-27-3, Heroin 951-77-9, Deoxycytidine 951-78-0, 2'-Deoxyuridine 3056-17-5, d4T 4097-22-7, 2',3'-Dideoxyadenosine 6742-12-7, Formycin A 7481-89-2, DdC 13877-76-4, Formycin B 18417-89-5, Sangivamycin 25526-93-6 29908-03-0, S-Adenosyl-L-methionine 30516-87-1, AZT 36791-04-5, Ribavirin 59277-89-3, Acyclovir 60129-59-1, Deoxytubercidin 69655-05-6, DdI 75607-67-9, Fludarabine phosphate 82410-32-0, Ganciclovir 118353-05-2, Carbovir 127779-20-8, Saquinavir 134678-17-4, 3TC 136470-78-5, Abacavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 174484-41-4, Tipranavir 192725-17-0, **Lopinavir** 198904-31-3, Atazanavir
RL: ANT (Analyte); ANST (Analytical study)
(nonpeptide **immunol**. **tracer** precursors comprising tyrosyl-(X)n-lysine or lysyl-(X)n-tyrosine motif, preparation method, and use for **immunoassays**)

IT 50-36-2D, Cocaine, derivs., conjugates 50-44-2D, 6-MP, conjugates 50-89-5D, Thymidine, conjugates, biological studies 50-91-9D, FdUrd, conjugates 51-21-8D, 5-Fluorouracil, conjugates 53-79-2D, Puromycin, conjugates 57-27-2D, Morphine, derivs., conjugates 58-61-7D, Adenosine, conjugates, biological studies 58-63-9D, Inosine, conjugates 58-85-5D, Biotin, complexes with (strept)avidin, conjugates 58-96-8D, Uridine, conjugates 65-46-3D, Cytidine, conjugates 69-33-0D, Tubercidine, conjugates 73-03-0D, Cordycepine, conjugates 91-19-0D, Quinoxaline, conjugates 118-00-3D, Guanosine, conjugates, biological studies 147-94-4D, Cytosine-β-D-arabinoside, conjugates 561-27-3D, Heroin, derivs., conjugates 951-77-9D, Deoxycytidine, conjugates 951-78-0D, 2'-Deoxyuridine, conjugates 3056-17-5D, d4T, peptide conjugates, iodo-125 labeled 4097-22-7D, Dideoxyadenosine, peptide conjugates, iodo-125 labeled 6742-12-7D, Formycin A, conjugates 9001-78-9D, Alkaline phosphatase, conjugates 9002-13-5D, Urease, conjugates 9003-99-0D, Peroxidase, conjugates 9013-20-1D, Streptavidin, complexes with biotin, conjugates 10028-17-8D, Tritium, conjugates 13877-76-4D, Formycin B, conjugates 14158-31-7D, Iodine-125, conjugates, biological studies 18417-89-5D, Sangivamycin, conjugates 25526-93-6D, conjugates 29908-03-0D, S-Adenosyl-L-methionine, conjugates 30516-87-1D, AZT, peptide conjugates, iodo-125 labeled 35978-98-4D, Lysyltyrosine, hapten conjugates 36791-04-5D, Ribavirin, conjugates 54925-88-1D, hapten conjugates 59277-89-3D, Acyclovir, conjugates 60129-59-1D, Deoxytubercidin, conjugates 75607-67-9D, Fludarabine phosphate, conjugates 82410-32-0D, Ganciclovir, conjugates 118353-05-2D, Carbovir, conjugates 127779-20-8D, Saquinavir, peptide conjugates, iodo-125 labeled 134678-17-4D, 3TC, peptide conjugates, iodo-125 labeled 136470-78-5D, Abacavir, conjugates 150378-17-9D, Indinavir, peptide conjugates, iodo-125 labeled 154598-52-4D, Efavirenz, conjugates 155213-67-5D, Ritonavir, peptide conjugates, iodo-125 labeled 159989-64-7D, Nelfinavir, peptide conjugates, iodo-125 labeled 161814-49-9D, Amprenavir, conjugates 174484-41-4D, Tipranavir, conjugates 192725-17-0D, **Lopinavir**, conjugates 198904-31-3D, Atazanavir, conjugates
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(nonpeptide **immunol**. **tracer** precursors comprising tyrosyl-(X)n-lysine or lysyl-(X)n-tyrosine motif, preparation method, and use for **immunoassays**)

L19 ANSWER 16 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:718892 HCAPLUS
DOCUMENT NUMBER: 139:270344
TITLE: Clinical, immunological and virological response to

different antiretroviral regimens in a cohort of HIV-2-infected patients
AUTHOR(S): van der Ende, Marchina E.; Prins, Jan M.; Brinkman, Kees; Keuter, Monique; Veenstra, Jan; Danner, Sven A.; Niesters, Hubert G. M.; Osterhaus, Albert D. M. E.; Schutten, Martin
CORPORATE SOURCE: Department of Internal Medicine, University Hospital Rotterdam, Rotterdam, Neth.
SOURCE: AIDS (London, United Kingdom) (**2003**), 17(Suppl. 3), S55-S61
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To assess the clin., **immunol**. and virol. response and the emergence of resistance towards antiretroviral therapy (ART) in a cohort of HIV-2-infected patients. Design: Observational study. Patients: HIV-2-infected patients residing in the Netherlands. Results: From 1995 to 2001 seven patients failed various ART regimens. The resistance mutations were analyzed retrospectively. Development of mutations proved to be similar to that observed in HIV-1-infected patients, with the exception of a higher occurrence of the Q151 M mutation within the reverse transcriptase gene. In a prospective study, comprising 13 consecutive naive HIV-2-infected patients, all patients achieved plasma HIV-2-RNA suppression below the detection limit (500 copies/mL). The antiretroviral regimen consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and indinavir, with a boosting dose of ritonavir; the median follow-up was 91 wk. Two patients experienced a temporary virol. rebound, while at the same time therapeutic drug monitoring showed sub-therapeutic plasma levels of indinavir. Conclusion: Sustained viral suppression in HIV-2-infected patients can be achieved using an antiretroviral regimen of two NRTIs and boosted indinavir or **lopinavir**.
CC 1-5 (Pharmacology)
Section cross-reference(s): 3, 10
IT 3056-17-5, Stavudine 30516-87-1, Zidovudine 69655-05-6, Didanosine 127779-20-8, Saquinavir 134678-17-4, Lamivudine 136470-78-5, Abacavir 147127-20-6, Tenofovir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 192725-17-0, **Lopinavir**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin., **immunol**. and virol. response to different antiretroviral regimens in HIV-2-infected patients)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 17 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:713323 HCAPLUS
DOCUMENT NUMBER: 140:87022
TITLE: In vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**
AUTHOR(S): Gonzalez, Luis M. F.; Brindeiro, Rodrigo M.; Tarin, Michelle; Calazans, Alexandre; Soares, Marcelo A.; Cassol, Sharon; Tanuri, Amilcar
CORPORATE SOURCE: Laboratorio de Virologia Molecular, Departmento de Genetica, Universidade Federal do Rio de Janeiro, CCS, Bloco A, Cidade Universitaria, Ilha do Fundao, Rio de Janeiro, 21944-970, Brazil

SOURCE: Antimicrobial Agents and Chemotherapy (**2003**), 47(9), 2817-2822
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In order to characterize the impact of genetic polymorphisms on the susceptibility of subtype C strains of human **immunodeficiency** virus type 1 to protease inhibitors (PIs), a subtype B protease that originated from an infectious clone was modified through site-directed mutagenesis to include the amino acid residue signatures of subtype C viruses (I15V, M36I, R41K, H69K, L89 M) with (clone C6) or without (clone C5) an I93L polymorphism present as a mol. signature of the worldwide subtype C protease. Their susceptibilities to com. available. PIs were measured by a recombinant virus phenotyping assay. We could not detect any differences in the 50% inhibitory concentration (IC50s) of amprenavir, indinavir, ritonavir, saquinavir, and nelfinavir for the clones analyzed. However, we did observe hypersusceptibility to **lopinavir** solely in clone C6, which includes the I93L substitution (a 2.6-fold decrease in the IC50 compared to that for the subtype B reference strain). The same phenotypic behavior was observed for 11 Brazilian and South African clin. isolates tested, in which only subtype C isolates carrying the I93L mutation presented significant hypersusceptibility to **lopinavir**.

CC 1-2 (Pharmacology)

IT Protein sequences
(alignment; in vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**)

IT Anti-AIDS agents
Genetic polymorphism
Human
Human groups
Human **immunodeficiency** virus 1
Phenotypes
Susceptibility (genetic)
(in vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**)

IT Mutation
(substitution; in vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**)

IT 144114-21-6, HIV Proteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**)

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro hypersusceptibility of human **immunodeficiency** virus type 1 subtype C protease to **lopinavir**)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 18 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:699811 HCAPLUS
DOCUMENT NUMBER: 139:270334
TITLE: Virological success of lopinavir/ritonavir salvage

regimen is affected by an increasing number of lopinavir/ritonavir-related mutations
AUTHOR(S): Bongiovanni, Marco; Bini, Teresa; Adorni, Fulvio; Meraviglia, Paola; Capetti, Amedeo; Tordato, Federica; Cicconi, Paola; Chiesa, Elisabetta; Cordier, Laura; Cargnel, Antonietta; Landonio, Simona; Rusconi, Stefano; Monforte, Antonella d'Arminio
CORPORATE SOURCE: Institute of Infectious Diseases and Tropical Medicine, University of Milan, Milan, Italy
SOURCE: Antiviral Therapy (**2003**), 8(3), 209-214
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We evaluated the virol. outcome of lopinavir/ritonavir (LPV/RTV) in 224 HIV-1-infected and protease inhibitor (PI)-experienced patients showing virol. failure to a highly active antiretroviral therapy (HAART) regimen and followed up for at least 3 mo. At baseline, the median level of plasma viremia was 4.61 log10 copies/mL (range 3-6.48) and the median CD4 cell count was 219 cells/mm3 (range 1-836). During a median follow-up of 272 days (range 92-635), we observed an increase in the number of CD4 cells (P=0.02) and a dramatic decrease in plasma viremia levels (P=0.0001), which became undetectable in 122 patients (54.5%). The closely related predictive factors were baseline plasma viremia levels and the number of mutations known to reduce susceptibility to LPV/RTV. Thirty-one patients (13.8%) discontinued LPV/RTV during the follow-up, and one AIDS event and three deaths were recorded. Of the 134 patients (59.8%) who underwent a baseline genotype resistance test, 22 (16.4%) had ≥6 mutations known to reduce LPV/RTV susceptibility; plasma viremia became undetectable in 76 patients (56.7%), only five of whom harbored ≥6 mutations at baseline (P=0.0001). The independent predictive factors related to virol. success were plasma viremia levels and the number of mutations reducing susceptibility to LPV/RTV at baseline; each addnl. log10 copies/mL of HIV RNA reduced the probability of virol. success by 34.0% and each extra mutation by 14.5%.
CC 1-5 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
CD4-positive T cell
Genotypes
Human
Human **immunodeficiency** virus 1
Mutation
(virol. success of **lopinavir**/ritonavir salvage regimen is affected by an increasing number of **lopinavir**/ritonavir-related mutations)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 19 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:688136 HCAPLUS
DOCUMENT NUMBER: 140:104598
TITLE: The impact of highly active antiretroviral therapy by the oral route on the CD8 subset in monkeys infected chronically with SHIV89.6P
AUTHOR(S): Yoshimura, Kazuhisa; Ido, Eiji; Akiyama, Hisashi; Kimura, Tetsuya; Aoki, Manabu; Suzuki, Hajime; Mitsuya, Hiroaki; Hayami, Masanori; Matsushita, Shuzo
CORPORATE SOURCE: Center for AIDS Research, Division of Clinical

Retrovirology and Infectious Diseases, Kumamoto University, Kumamoto, 860-0811, Japan
SOURCE: Journal of Virological Methods (**2003**), 112(1-2), 121-128
CODEN: JVMEDH; ISSN: 0166-0934
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of this study was to assess the impact of highly active antiretroviral therapy (HAART) by an oral route on the peripheral blood CD8 subset in the monkeys infected persistently with a pathogenic strain, SHIV89.6P. Two rhesus macaques were inoculated i.v. with SHIV89.6P, then treated with the combination of AZT, 3TC and **Lopinavir**/Ritonavir (LPV/RTV) as recommended in humans by the oral route with confectionery continued for 28 days. In one of two chronically infected macaques, MM260, the viral load was maintained in the range of 104-105 copies/mL before HAART. The plasma viral load and proviral DNA decreased dramatically during the treatment, and cessation of this therapy the viral load rebounded to the pre-treatment level but the proviral DNA rebound was delayed. The other monkey, MM242, had low viral loads (1.2+103-<5+102 copies/mL) both before and after HAART. CD4+ and CD8+ T cell counts and proviral DNA level were not significantly changed after the treatment. The percentages of CD8+CD45RA-Ki67+cells increased during (MM260) or after (MM242) HAART and the subset was maintained at a high percentage until 18 wk post HAART in MM242. These findings suggest that this primate model might serve an important role in testing the virol. and **immunol**. efficacy of novel therapeutic strategies combined with HAART.
CC 1-6 (Pharmacology)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 20 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:625950 HCAPLUS
DOCUMENT NUMBER: 140:192242
TITLE: Characterization of resistant HIV variants generated by in vitro passage with lopinavir/ritonavir
AUTHOR(S): Mo, Hongmei; Lu, Liangjun; Dekhtyar, Tatyana; Stewart, Kent D.; Sun, Eugene; Kempf, Dale J.; Molla, Akhteruzzaman
CORPORATE SOURCE: Department R47D, Global Pharmaceutical Research Development, Abbott Laboratories, Abbott Park, IL, 60064-6217, USA
SOURCE: Antiviral Research (**2003**), 59(3), 173-180
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lopinavir (LPV, formerly ABT-378) is an HIV protease inhibitor (PI) that is co-administered with a small amount of ritonavir (RTV), which greatly increases and sustains the plasma levels of LPV. Lopinavir/ritonavir (LPV/r) has shown potent antiviral activity in both therapy-naive and PI-experienced patients. To assess the effect of pharmacol. relevant ratios of LPV/RTV (LPV/r) on the emergence of resistant HIV in vitro, HIV-1 pNL4-3 was passaged in the presence of increasing concns. of LPV alone and LPV/r. Passages with fixed 5/1 and 15/1 concentration ratios of LPV/r
initially selected I84V and I50V/M46I mutants, resp. Selection with LPV alone also generated the same initial mutants (I50V/M46I) as the 15/1

LPV/r passage. Further passage produced other mutations previously found to be associated with PI-resistance. Phenotypic susceptibility to both LPV and RTV decreased with successive passages, irresp. of whether RTV was present in the selection experiment Furthermore, in the two selection expts. that included RTV (at either 5/1 or 15/1 LPV/r ratio), the IC50 of RTV at each passage evaluated was at least five-fold higher than the concentration of RTV employed at that passage, while the IC50 of LPV toward the passaged virus was similar to the concentration of LPV used at that passage, indicating that the selective pressure was attributable to LPV and not RTV.

CC 1-5 (Pharmacology)

IT AIDS (disease)
Anti-AIDS agents
Antiviral agents
Human
Human **immunodeficiency** virus 1
(characterization of resistant HIV variants generated by in vitro passage with **lopinavir**/ritonavir)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 21 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:612275 HCAPLUS
DOCUMENT NUMBER: 140:87106
TITLE: Pol Gene Sequence Variation in Swedish HIV-2 Patients Failing Antiretroviral Therapy
AUTHOR(S): Brandin, Eleonor; Lindborg, Lena; Gyllensten, Katarina; Brostroem, Christina; Hagberg, Lars; Gisslen, Magnus; Tuvesson, Bjoern; Blaxhult, Anders; Albert, Jan
CORPORATE SOURCE: Karolinska Institute, Department of Laboratory Medicine, Division of Clinical Virology, Huddinge University Hospital, Huddinge/Stockholm, S-141 86, Swed.
SOURCE: AIDS Research and Human Retroviruses (**2003**), 19(7), 543-550
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There is limited knowledge about how to treat and interpret results from genotypic resistance assays in HIV-2 infection. Here, genetic variation in HIV-2 pol gene was studied in 20 of 23 known HIV-2 cases in Sweden. Five patients with signs of virol. treatment failure were longitudinally studied. Clin., virol. and **immunol**. data were collected and the protease (PR) and first half of the reverse transcriptase (RT) was amplified and directly sequenced from plasma samples. Moderate to extensive genetic evolution was observed in four of the five patients who failed treatment. Some mutations occurred at positions known to confer resistance in HIV-1, but many occurred at other positions in PR and RT. All patients had been treated with zidovudine alone or in combination with other antiretroviral drugs, but none displayed a mutation at position 215, which is the primary zidovudine resistance site in HIV-1. Instead, a E219D mutation evolved in virus from two patients and a Q151M mutation evolved in two other patients. A M184V mutation indicative of lamivudine resistance was detected in three patients. The virus of one patient who had been treated with ritonavir, nelfinavir, and **lopinavir** successively acquired nine unusual mutations in the protease gene, most of which are not considered primary or secondary resistance mutations in HIV-1. Our data indicate that the evolutionary pathways that lead to

antiretroviral resistance in HIV-2 and HIV-1 exhibit both similarities and differences. Genotypic HIV-2 resistance assays cannot be interpreted using algorithms developed for HIV-1, instead new algorithms specific for HIV-2 have to be developed.
CC 1-5 (Pharmacology)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 22 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:599973 HCAPLUS
DOCUMENT NUMBER: 140:122004
TITLE: Lopinavir Plasma Concentrations and Changes in Lipid Levels During Salvage Therapy with Lopinavir/Ritonavir-Containing Regimens
AUTHOR(S): Gutierrez, Felix; Padilla, Sergio; Navarro, Andres; Masia, Mar; Hernandez, Ildefonso; Ramos, Jose; Esteban, Angel; Martin-Hidalgo, Alberto
CORPORATE SOURCE: Internal Medicine Department, Infectious Diseases Unit, Hospital General Universitario de Elche, Alicante, Spain
SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (**2003**), 33(5), 594-600
CODEN: JJASFJ; ISSN: 1525-4135
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB OBJECTIVE: To determine whether an association existed between lopinavir (LPV) plasma concns. and changes in lipid levels. DESIGN: A prospective, nonrandomized study. SUBJECTS HIV-infected subjects with virol. failure on protease inhibitor-containing regimens. Twenty-two consecutive patients were enrolled, 19 completed 24 wk of treatment, and 16 completed the full 48-wk study period. INTERVENTION: Patients were treated with LPV/ritonavir (LPV/r) in combination with other antiretroviral agents. Subjects were evaluated at baseline and weeks 4, 8, 12, 24, 36, and 48. LPV trough plasma concns. and lipid levels were measured. RESULTS: LPV trough concns. were higher in patients experiencing grade 3 or higher lipid elevations (mean [SD]: 9.71 μg/mL (5.62) vs. 6.09 μg/mL (3.83); P = 0.002) and in those developing grade 2 or higher hypercholesterolemia (mean [SD]: 8.48 μg/mL [4.64] vs. 5.71 μg/mL [3.94]; P = 0.003). All patients developing grade 2 or higher cholesterol elevation had an LPV trough concentration at week 4 greater than 8 μg/mL. Significant pos. correlations were found between LPV trough concns. and changes in triglyceride and cholesterol levels. CONCLUSIONS: In patients receiving salvage therapy with LPV/r, there is an association between LPV plasma concns. and lipid changes. Patients achieving higher LPV trough concns. may be at greater risk of experiencing dyslipidemia. Further investigations are warranted to support a direct cause and effect relationship.
CC 1-2 (Pharmacology)
IT Anti-AIDS agents
Human
Human **immunodeficiency** virus
Hypercholesterolemia
(**lopinavir** plasma concns. and changes in lipid levels during salvage therapy with **lopinavir**/ritonavir-containing regimens)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 23 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:592874 HCAPLUS
DOCUMENT NUMBER: 140:70351
TITLE: HIV-1 Phenotypic Susceptibility to Lopinavir (LPV) and Genotypic Analysis in LPV/r-Naive Subjects With Prior Protease Inhibitor Experience
AUTHOR(S): Monno, Laura; Saracino, Annalisa; Scudeller, Luigia; Pastore, Giuseppe; Bonora, Stefano; Cargnel, Antonietta; Carosi, Gianpiero; Angarano, Gioacchino
CORPORATE SOURCE: Clinic of Infectious Diseases, University of Bari, Bari, 70124, Italy
SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (2003), 33(4), 439-447
CODEN: JJASFJ; ISSN: 1525-4135
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relationship between phenotypic susceptibility to lopinavir (LPV) and genotypic pattern was investigated in LPV-naive, protease inhibitor (PI)-experienced subjects. Protease sequences of 100 HIV isolates with ascertained susceptibility (determined by Antivirogram) to LPV were analyzed (VircoGen). Two different thresholds (2.5- and 10-fold) were used for defining reduced susceptibility. Mutations were classified as LPV/r (the actual formulation of LPV that combines LPV with low-dose ritonavir) mutations according to the International AIDS Society-USA. Thirty-four isolates showed reduced LPV susceptibility (2.6- to 75.9-fold). Fold resistance to LPV correlated with the number of total and LPV/r mutations (Spearman coefficient = 0.62 and 0.74, resp.; P < 0.001). Current PI therapy (P = 0.002) and indinavir administration (P < 0.001), >5 LPV/r mutations (P < 0.0012), and detection of L10FIRV, K20MR, M46IL, I54VL, A71VT, G73SA, V82AFTS, I84V, and M90L were associated with LPV resistance in univariate anal. Factors independently associated with LPV resistance were K20MR (odds ratio [OR], 13.9; 95% confidence interval [CI], 1.3-145.1; P = 0.028), I54VL (OR, 131.7; 95% CI, 10.5-1654.7; P < 0.001), G73SA (OR, 19.2; 95% CI, 1.4-273.7; P = 0.029), and I84V (OR, 177.5; 95% CI, 6.0-5232.5; P = 0.003) mutations and >9 protease mutations (OR, 18.6; 95% CI, 1.6-213.0; P = 0.019). Sixteen of 34 and 18 of 34 isolates with reduced LPV susceptibility showed >10-fold or <10-fold LPV resistance, resp. Linear regression anal. demonstrated that each addnl. LPV mutation and I54VL accounted for much of the fold resistance to LPV (adjusted R2 = 0.70). In conclusion, for PI-experienced patients requiring salvage therapy, switching to LPV should be based on the number of baseline mutations and the presence of mutation 54.

CC 1-5 (Pharmacology)
IT Genotypes
Human
Human **immunodeficiency** virus 1
Mutation
(HIV-1 phenotypic susceptibility to **lopinavir** and genotypic anal. in **lopinavir** naive subjects with prior protease inhibitor experience)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 24 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:577520 HCAPLUS
DOCUMENT NUMBER: 139:207159
TITLE: Immunological recovery despite virological failure is independent of human immunodeficiency virus-type 1 resistant mutants in children receiving highly active

antiretroviral therapy
AUTHOR(S): Chiappini, Elena; Galli, Luisa; Zazzi, Maurizio; de Martino, Maurizio
CORPORATE SOURCE: Division of Paediatrics and Infectious Diseases, Department of Paediatrics, University of Florence, Florence, Italy
SOURCE: Journal of Medical Virology (**2003**), 70(4), 506-512
CODEN: JMVIDB; ISSN: 0146-6615
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Relationships between human immunodeficiency virus-type-1 (HIV-1) drug-resistant mutants and immunol. recovery were investigated after 12-wk antiretroviral therapy in 43 children infected perinatally with virol. failure. Twenty-two children received highly active antiretroviral therapy (HAART) and 21 received double therapy with reverse transcriptase inhibitors. At baseline, no difference in reverse transcriptase or protease inhibitors resistant mutants was present among the groups. After 12 wk, the two groups were similar regarding proportion of children with reverse transcriptase resistant mutants. Sixteen (73%) HAART-treated children, but no child receiving double therapy had HIV-1 with primary resistance mutations to protease inhibitors. Secondary protease mutations were found in all HAART-treated and in 17/21 (81%) children receiving double therapy. The mutation nos. in reverse transcriptase or protease genes were significantly higher after HAART than after double therapy. Nevertheless, 12 (55%) of HAART-treated children (but no child receiving double therapy) showed immunol. recovery. The frequency and number of mutations were similar in HAART-treated children with or without immunol. recovery both at baseline and after 12 wk. The findings suggest, immunol. recovery notwithstanding, virol. failure is independent of drug-resistant mutations and consequent possible changes in viral fitness.
CC 1-5 (Pharmacology)
IT 3056-17-5, Stavudine 7481-89-2, Zalcitabine 69655-05-6, Didanosine 129618-40-2, Nevirapine 134678-17-4, Lamivudine 136470-78-5, Abacavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 192725-17-0, **Lopinavir**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**immunol**. recovery despite virol. failure is independent of human **immunodeficiency** virus-type 1 resistant mutants in children receiving highly active antiretroviral therapy)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 25 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:455182 HCAPLUS
DOCUMENT NUMBER: 139:223785
TITLE: Dual pressure from antiretroviral therapy and cell-mediated immune response on the human immunodeficiency virus type 1 protease gene
AUTHOR(S): Karlsson, Annika C.; Deeks, Steven G.; Barbour, Jason D.; Heiken, Brandon D.; Younger, Sophie R.; Hoh, Rebecca; Lane, Meghan; Saellberg, Matti; Ortiz, Gabriel M.; Demarest, James F.; Liegler, Teri; Grant, Robert M.; Martin, Jeffrey N.; Nixon, Douglas F.
CORPORATE SOURCE: Gladstone Int. of Virology and Immunology, Univ. of California, San Francisco, CA, 94141, USA
SOURCE: Journal of Virology (**2003**), 77(12),

6743-6752
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human immunodeficiency virus (HIV)-specific CD8+ T-lymphocyte pressure can lead to the development of viral escape mutants, with consequent loss of immune control. Antiretroviral drugs also exert selection pressures on HIV, leading to the emergence of drug resistance mutations and increased levels of viral replication. The authors have determined a minimal epitope of HIV protease, amino acids 76 to 84, towards which a CD8+ T-lymphocyte response is directed. This epitope, which is HLA-A2 restricted, includes two amino acids that commonly mutate (V82A and I84V) in the face of protease inhibitor therapy. Among 29 HIV-infected patients who were treated with protease inhibitors and who had developed resistance to these drugs, the authors show that the wild-type PR82V76-84 epitope is commonly recognized by cytotoxic T lymphocytes (CTL) in HLA-A2- pos. patients and that the CTL directed to this epitope are of high avidity. In contrast, the mutant PR82A76-84 epitope is generally not recognized by wild-type-specific CTL, or when recognized it is of low to moderate avidity, suggesting that the protease inhibitor-selected V82A mutation acts both as a CTL and protease inhibitor escape mutant. Paradoxically, the absence of a mutation at position 82 was associated with the presence of a high-avidity CD8+ T-cell response to the wild-type virus sequence. The results indicate that both HIV type 1-specific CD8+ T cells and antiretroviral drugs provide complex pressures on the same amino acid sequence of the HIV protease gene and, thus, can influence viral sequence evolution.
CC 1-5 (Pharmacology)
Section cross-reference(s): 15
IT 3056-17-5, Stavudine 30516-87-1, Zidovudine 69655-05-6, Didanosine 127779-20-8, Saquinavir 129618-40-2, Nevirapine 134678-17-4, Lamivudine 136470-78-5, Abacavir 147127-20-6, Tenofovir 150378-17-9, Indinavir 154598-52-4, Efavirenz 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (antiretroviral therapy- and immune-driven escape by **immunodeficiency** virus from cytotoxic T-cell response to HIV-1 protease)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 26 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:438815 HCAPLUS
DOCUMENT NUMBER: 140:22551
TITLE: Simultaneous determination of the HIV Drugs indinavir, amprenavir, saquinavir, ritonavir, lopinavir, nelfinavir, the nelfinavir hydroxymetabolite M8, and nevirapine in human plasma by reversed-phase high-performance liquid chromatography
AUTHOR(S): Droste, J. A. H.; Verweij-van Wissen, C. P. W. G. M.; Burger, D. M.
CORPORATE SOURCE: Department of Clinical Pharmacy, University Medical Center, Nijmegen, Neth.
SOURCE: Therapeutic Drug Monitoring (**2003**), 25(3), 393-399
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal

LANGUAGE: English
AB A reversed-phase high-performance liquid chromatog. method for the simultaneous quant. determination of the currently available HIV protease inhibitors amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, the active nelfinavir metabolite M8, and the nonnucleoside reverse transcriptase inhibitor nevirapine in human plasma is described. The method involved liquid-liquid extraction from plasma, followed by high-performance liquid chromatog. with an OmniSpher 5 C18 column and UV detection set at a wavelength of 215 nm for the protease inhibitors and 280 nm for nevirapine. The runtime was 25 min. The assay has been validated over the concentration range of 0.05 to 30 mg/L for indinavir, nelfinavir, ritonavir, and saquinavir, 0.07 to 30 mg/L for amprenavir and lopinavir, and 0.05 to 15 mg/L for M8 and nevirapine. This method proved to be simple, accurate, and precise and is useful for the therapeutic drug monitoring of protease inhibitors and the nonnucleoside reverse transcriptase inhibitor nevirapine on a routine basis.
CC 1-1 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
Blood analysis
Human
Human **immunodeficiency** virus
Reversed phase HPLC
(simultaneous determination of the HIV drugs indinavir, amprenavir, saquinavir,
ritonavir, **lopinavir**, nelfinavir, velfinavir
hydroxymetabolite M8, and nevirapine in human plasma by reversed-phase high-performance liquid chromatog.)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 27 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:359371 HCAPLUS
DOCUMENT NUMBER: 139:78307
TITLE: Lopinavir/ritonavir: A review of its use in the management of HIV infection
AUTHOR(S): Cvetkovic, Risto S.; Goa, Karen L.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (**2003**), 63(8), 769-802
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. **Lopinavir** is a novel protease inhibitor (PI) developed from ritonavir. Coadministration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of **lopinavir** against HIV-1 protease. Coformulated **lopinavir**/ritonavir was developed for ease of administration and to ensure both drugs are taken together, as part of combination therapy with other antiretroviral agents. Coformulated **lopinavir** /ritonavir-based regimens provide adequate and durable suppression of viral load and sustained improvements in CD4+ cell counts, as demonstrated in randomized trials in antiretroviral therapy-naive and -experienced adults and children. To date, development of primary resistance to **lopinavir**/ritonavir has not been observed in 470 antiretroviral therapy-naive patients treated for >48 wk. The **lopinavir** /ritonavir-based regimen was more effective than nelfinavir in antiretroviral therapy-naive HIV-1-infected patients in a phase III trial. The coformulation is also effective as "salvage" therapy, as shown by low

cross-resistance rates in patients who failed to respond to treatment with other PIs in phase II trials. Coformulated **lopinavir**/ritonavir was well tolerated in both antiretroviral therapy-naive and -experienced HIV-1-infected adults and children with low rates of study drug-related treatment discontinuations. The most common adverse event in adults associated with **lopinavir**/ritonavir was diarrhea, followed by other gastrointestinal disturbances, asthenia, headache and skin rash. The incidence of moderate-to-severe adverse events in children was low, skin rash being the most common. Changes in body fat composition occurred with equal frequency in **lopinavir**/ritonavir- and nelfinavir-treated naive patients, through week 60 in a phase III study. Although laboratory abnormalities occurred with similar frequency in both treatment groups, triglycerides grade 3/4 elevations were significantly more frequent with **lopinavir**/ritonavir. Total cholesterol and triglycerides grade 3/4 elevations appear to occur more frequently in PI-experienced than in PI-naive **lopinavir**/ritonavir-treated patients. A number of clin. important drug interactions have been reported with **lopinavir** /ritonavir necessitating dosage adjustments of **lopinavir** /ritonavir and/or the interacting drugs, and several other drugs are contraindicated in patients receiving the coformulation. Coformulated **lopinavir**/ritonavir is a novel PI that, in combination with other antiretroviral agents, suppresses plasma viral load and enhances **immunol**. status in therapy-naive and -experienced patients with HIV-1 infection. **Lopinavir**/ritonavir appears more effective than nelfinavir in "naive" patients and is also suitable for "salvage" therapy, because of its high barrier to development of resistance. Given its clin. efficacy, a tolerability profile in keeping with this class of drugs, favorable resistance profile and easy-to-adhere-to administration regimen, coformulated **lopinavir**/ritonavir should be regarded as a first-line option when including a PI in the management of HIV-1 infection.

CC 1-0 (Pharmacology)

IT Anti-AIDS agents
Drug interactions
Human
Human **immunodeficiency** virus 1
(coformulated **lopinavir** and ritonavir for the treatment of HIV infection)

REFERENCE COUNT: 150 THERE ARE 150 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 28 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:343888 HCAPLUS
DOCUMENT NUMBER: 139:301355
TITLE: Decrease in LDL size in HIV-positive adults before and after lopinavir/ritonavir-containing regimen: an index of atherogenicity?
AUTHOR(S): Badiou, S.; Merle De Boever, C.; Dupuy, A. M.; Baillat, V.; Cristol, J. P.; Reynes, J.
CORPORATE SOURCE: Department of Biochemistry, University Hospital, Montpellier, 34295, Fr.
SOURCE: Atherosclerosis (Shannon, Ireland) (**2003**), 168(1), 107-113
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypertriglyceridemia (HTG) is frequently observed during highly active

antiretroviral therapy (HAART) including protease inhibitor. Apolipoprotein (apo)CIII could be involved in this HTG by inhibition of triglyceride (TG) hydrolysis, which leads to the occurrence of small dense low d. lipoprotein (sdLDL), a recognized cardiovascular risk factor. Objective was to characterize the influence of lopinavir/ritonavir-containing regimen on lipoprotein profile. 24 Antiretroviral-experienced HIV infected adults (including 14 patients in therapeutic interruption of at least 2 mo) and 14 HIV uninfected healthy controls were enrolled. Serum lipid parameters (total cholesterol (TC), HDL-C, LDL-C, TG, apoA1, apoB, apoCIII), lipoprotein composition and LDL size were determined before initiation of lopinavir/ritonavir-containing regimen, and at 1 and 3 mo thereafter. At baseline an atherogenic lipid profile was evidenced, characterized by a moderate HTG associated to a smaller mean LDL size (25.16 vs. 25.93 nm, P<0.001), an enrichment in TG of LDL (11.4 vs. 6.0%, P<0.01) and a high prevalence of sdLDL (75 vs. 7%, P<0.01) when compared to controls. After 1 mo of lopinavir/ritonavir-containing regimen, a significant reduction of LDL size (24.81 vs. 25.16 nm, P<0.05) and a significant increase in cholesterol total (5.53 vs. 4.49 mmol/l, P<0.001), in TG (4.20 vs. 2.01 mmol/l, P<0.001), in apoA1 (1.28 vs. 1.11 g/l, P<0.001), in apoB (1.08 vs. 0.94 g/l, P<0.01), in apoCIII (0.16 vs. 0.10 g/l, P<0.001), in TG percentage in LDL (14.4 vs. 11.4, P<0.05) and in TG percentage in HDL (10.2 vs. 8.3, P<0.05) were observed Advanced stage of HIV infection is associated with an atherogenic lipid profile including a high prevalence of sdLDL. Lopinavir/ritonavir-containing regimen accentuates the reduction of LDL size. Since fibrates decrease TG and increase LDL size, they appear as a logical option to manage HAART-induced HTG.

CC 1-5 (Pharmacology)

IT AIDS (disease)
Anti-AIDS agents
Antiviral agents
Atherosclerosis
Human
Human **immunodeficiency** virus 1
Hypertriglyceridemia
(decrease in LDL size in HIV-pos. adults before and after **lopinavir**/ritonavir-containing regimen)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 29 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:288959 HCAPLUS
DOCUMENT NUMBER: 139:30239
TITLE: Determining the relative efficacy of highly active antiretroviral therapy
AUTHOR(S): Louie, Michael; Hogan, Christine; Di Mascio, Michele; Hurley, Arlene; Simon, Viviana; Rooney, James; Ruiz, Nancy; Brun, Scott; Sun, Eugene; Perelson, Alan S.; Ho, David D.; Markowitz, Martin
CORPORATE SOURCE: Aaron Diamond AIDS Research Center, The Rockefeller University, New York, NY, USA
SOURCE: Journal of Infectious Diseases (**2003**), 187(6), 896-900
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Despite the clin. benefits of combination antiviral therapy, whether maximal antiviral potency has been achieved with current drug combinations

remains unclear. We studied the first phase of decay of human **immunodeficiency** virus type 1 (HIV-1) RNA in plasma, one early indicator of antiviral activity, after the administration of a novel combination of **lopinavir**/ritonavir, efavirenz, tenofovir disoproxil fumarate, and lamivudine and compared it with that observed in matched cohorts treated with alternative combination regimens. On the basis of these comparisons, we conclude that the relative potency of highly active antiretroviral therapy may be augmented by as much as 25%-30%. However, it is important to emphasize that further study is warranted to explore whether these early measurements of relative efficacy provide long-term virol. and clin. benefits. Nevertheless, we believe that optimal treatment regimens for HIV-1 have yet to be identified and that continued research to achieve this goal is warranted.

CC 1-5 (Pharmacology)
Section cross-reference(s): 10

IT Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
Virulence (microbial)
(efficacy of **lopinavir**/ritonavir, efavirenz, tenofovir and lamivudine combination in treatment of HIV)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 30 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:280502 HCAPLUS
DOCUMENT NUMBER: 139:111123
TITLE: Activities of atazanavir (BMS-232632) against a large panel of human immunodeficiency virus type 1 clinical isolates resistant to one or more approved protease inhibitors
AUTHOR(S): Colonno, Richard J.; Thiry, Alexandra; Limoli, Kay; Parkin, Neil
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA
SOURCE: Antimicrobial Agents and Chemotherapy (**2003**), 47(4), 1324-1333
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate the cross-resistance profile of the human **immunodeficiency** virus type 1 protease inhibitor (PI) atazanavir (BMS-232632), a panel of 551 clin. isolates exhibiting a wide array of PI resistance profiles and a variety of genotypic patterns were assayed for susceptibility to atazanavir and six other PIs: amprenavir, indinavir, **lopinavir**, nelfinavir, ritonavir, and saquinavir. In general, redns. in atazanavir susceptibility in vitro required several amino acid changes and were relatively modest in degree, and susceptibility was retained among isolates resistant to one or two of the currently approved PIs. There was a clear trend toward loss of susceptibility to atazanavir, as isolates exhibited increasing levels of cross-resistance to multiple PIs. Atazanavir appeared to have a distinct resistance profile relative to each of the other six PIs tested based on susceptibility comparisons against this panel of resistant isolates. Anal. of the genotypic profiles of 943 PI-susceptible and -resistant clin. isolates identified a strong correlation between the presence of amino acid changes at specific residues (10I/V/F, 20R/M/I, 24I, 33I/F/V, 36I/L/V, 46I/L, 48V, 54V/L, 63P, 71V/T/I, 73C/S/T/A, 82A/F/S/T, 84V, and 90M) and decreased susceptibility

to atazanavir. While no single substitution or combination of substitutions was predictive of atazanavir resistance (change, >3.0-fold), the presence of at least five of these substitutions correlated strongly with loss of atazanavir susceptibility. Mutations associated with reduced susceptibility to each of the other six PIs were also determined

CC 1-5 (Pharmacology)

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir** 198904-31-3, Atazanavir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activities of atazanavir (BMS-232632) against a large panel of human **immunodeficiency** virus type 1 clin. isolates resistant to one or more approved protease inhibitorsn)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 31 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:264181 HCAPLUS

DOCUMENT NUMBER: 139:332393

TITLE: Brief Report: Efficacy and Treatment-Limiting Toxicity With the Concurrent Use of Lopinavir/Ritonavir and a Third Protease Inhibitor in Treatment-Experienced HIV-Infected Patients

AUTHOR(S): Casau, Nathalie C.; Glesby, Marshall J.; Paul, Simon; Gulick, Roy M.

CORPORATE SOURCE: Div. International Med. and Infectious Diseases, Dep. Med., Weill Med. Coll. of Cornell Univ., New York, NY, USA

SOURCE: JAIDS, Journal of Acquired Immune Deficiency Syndromes (**2003**), 32(5), 494-498
CODEN: JJASFJ; ISSN: 1525-4135

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To investigate the efficacy and tolerability of using lopinavir/ritonavir concurrently with a third protease inhibitor (PI), the authors reviewed the medical records of 47 HIV-infected patients treated with antiretroviral regimens containing lopinavir/ritonavir and amprenavir, saquinavir, indinavir, or nelfinavir. The baseline mean HIV RNA level was 4.6 log10 copies/mL, and the median CD4 cell count was 123/mm3. By week 40, one patient (2%) was lost to follow-up, and 21 (44%) discontinued their lopinavir/ritonavir plus a third PI regimens: 4 (8%) due to virol. failure as determined by the clinician; 13 (28%) due to toxicity; and 4 (8%) due to social reasons. By intent-to-treat anal., 12 (26%) of 47 patients had an HIV RNA level of less than 400 copies/mL at 40 wk. By multivariate anal., factors associated with virol. response were no prior lopinavir exposure ($p = .03$) and no prior exposure to nonnucleoside reverse transcriptase inhibitors among patients taking a nonnucleoside reverse transcriptase inhibitor ($p = .05$). Some HIV-infected patients concurrently treated with lopinavir/ritonavir and a third PI have viral suppression; many eventually discontinue therapy because of toxicity or virol. failure.

CC 1-5 (Pharmacology)

IT AIDS (disease)
Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(efficacy and treatment-limiting toxicity with concurrent use of **lopinavir**/ritonavir and third protease inhibitor in

treatment-experienced HIV-infected patients)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 32 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:168473 HCAPLUS
DOCUMENT NUMBER: 138:331262
TITLE: Methods for integration of pharmacokinetic and phenotypic information in the treatment of infection with human immunodeficiency virus
AUTHOR(S): Acosta, Edward P.; King, Jennifer R.
CORPORATE SOURCE: Division of Clinical Pharmacology, University of Alabama at Birmingham, USA
SOURCE: Clinical Infectious Diseases (**2003**), 36(3), 373-377
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interest in monitoring antiretroviral drug concns. in human immunodeficiency virus-infected patients has gained considerable momentum in recent years. We present a potential method for integrating pharmacokinetic and phenotypic information that will assist clinicians in choosing optimal treatment regimens for their patients and that will provide an approach for the interpretation of antiretroviral plasma drug concns.
CC 1-5 (Pharmacology)
IT 127779-20-8, Saquinavir 129618-40-2, Nevirapine 150378-17-9, Indinavir 154598-52-4, Efavirenz 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for integration of pharmacokinetic and phenotypic information in the treatment of infection with human **immunodeficiency** virus)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 33 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:136347 HCAPLUS
DOCUMENT NUMBER: 138:280717
TITLE: Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection
AUTHOR(S): Csajka, Chantal; Marzolini, Catia; Fattinger, Karin; Decosterd, Laurent A.; Fellay, Jacques; Telenti, Amalio; Biollaz, Jerome; Buclin, Thierry
CORPORATE SOURCE: Division of Clinical Pharmacology and Division of Infectious Diseases, University Hospital, Lausanne, Switz.
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (**2003**), 73(1), 20-30
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: The reverse transcriptase inhibitor efavirenz is currently used at a fixed dose of 600 mg/d. However, dosage individualization based on plasma concentration monitoring might be indicated. This study aimed to assess

the efavirenz pharmacokinetic profile and interpatient vs. intrapatient variability in patients who are pos. for human immunodeficiency virus, to explore the relationship between drug exposure, efficacy, and central nervous system toxicity and to build up a Bayesian approach for dosage adaptation. Methods: The population pharmacokinetic anal. was performed by use of NONMEM based on plasma samples from a cohort of unselected patients receiving efavirenz. With the use of a 1-compartment model with first-order absorption, the influence of demog. and clin. characteristics on oral clearance and oral volume of distribution was examined The average drug exposure during 1 dosing interval was estimated for each patient and correlated with markers of efficacy and toxicity. The population kinetic parameters and the variabilities were integrated into a Bayesian equation for dosage adaptation based on a single plasma sample. Results: Data from 235 patients with a total of 719 efavirenz concns. were collected. Oral clearance was 9.4 L/h, oral volume of distribution was 252 L, and the absorption rate constant was 0.3 h-1. Neither the demog. covariates evaluated nor the comedications showed a clin. significant influence on efavirenz pharmacokinetics. A large interpatient variability was found to affect efavirenz relative bioavailability (coefficient of variation, 54.6%), whereas the intrapatient variability was small (coefficient of variation, 26%). An inverse correlation between average drug exposure and viral load and a trend with central nervous system toxicity were detected. This enabled the derivation of a dosing adaptation strategy suitable to bring the average concentration into a therapeutic target from 1000 to 4000 μg/L to optimize viral load suppression and to minimize central nervous system toxicity. Conclusions: The high interpatient and low intrapatient variability values, as well as the potential relationship with markers of efficacy and toxicity, support the therapeutic drug monitoring of efavirenz. However, further evaluation is needed before individualization of an efavirenz dosage regimen based on routine drug level monitoring should be recommended for optimal patient management.

CC 1-2 (Pharmacology)

IT 3056-17-5, Stavudine 30516-87-1, Zidovudine 69655-05-6, Didanosine 127779-20-8, Saquinavir 134678-17-4, Lamivudine 136470-78-5, Abacavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration has no influence on efavirenz pharmacokinetics; efavirenz population pharmacokinetics and effects in patients with human **immunodeficiency** virus infection)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 34 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:58128 HCAPLUS
DOCUMENT NUMBER: 138:105628
TITLE: Activated haptens comprising HIV protease inhibitor conjugates for raising antibodies useful in immunoassay
INVENTOR(S): Deras, Ina; Hui, Raymond; Sigler, Gerald F.; Huber, Erasmus J.; Von der Eltz, Herbert W.; Ghoshal, Mitali; Root, Richard Terry; Metz, Sigrun
PATENT ASSIGNEE(S): Roche Diagnostics G.m.b.H., Germany; F. Hoffmann-La Roche A.-G.
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006506	A2	20030123	WO 2002-EP7843	20020715 <--
WO 2003006506	A3	20031106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1409546	A2	20040421	EP 2002-754883	20020715
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005508877	T2	20050407	JP 2003-512276	20020715
PRIORITY APPLN. INFO.:			US 2001-305192P	P 20010713
			US 2002-192052	A 20020710
			WO 2002-EP7843	W 20020715

AB Activated **haptens** useful for generating **immunogens** to HIV protease inhibitors, **immunogens** useful for producing **antibodies** to HIV protease inhibitors, and **antibodies** and **labeled** conjugates useful in **immunoassays** for HIV protease inhibitors. The novel **haptens** feature an activated functionality at the central, non-terminal hydroxyl group common to all HIV protease inhibitors, e.g., saquinavir, nelfinavir, indinavir, amprenavir, ritonavir and **lopinavir**.

IC C07K014-81

CC 15-2 (Immunochemistry)
Section cross-reference(s): 1, 9

IT 155213-67-5DP, Ritonavir, conjugates 159989-64-7DP, Nelfinavir, conjugates 161814-49-9DP, Amprenavir, conjugates 192725-17-0DP, **Lopinavir**, conjugates
RL: ANT (Analyte); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(activated **haptens** comprising HIV protease inhibitor conjugates for raising **antibodies** useful in **immunoassay**)

L19 ANSWER 35 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:26959 HCAPLUS
DOCUMENT NUMBER: 139:30219
TITLE: Pharmacokinetic-pharmacodynamic analysis of **lopinavir**-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human **immunodeficiency** virus-infected patients
AUTHOR(S): Hsu, Ann; Isaacson, Jeffrey; Brun, Scott; Bernstein, Barry; Lam, Wayne; Bertz, Richard; Foit, Cheryl; Rynkiewicz, Karen; Richards, Bruce; King, Martin; Rode, Richard; Kempf, Dale J.; Granneman, G. Richard; Sun, Eugene

CORPORATE SOURCE: Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Antimicrobial Agents and Chemotherapy (**2003**), 47(1), 350-359
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The steady-state pharmacokinetics and pharmacodynamics of two oral doses of **lopinavir**-ritonavir (**lopinavir**/r; 400/100 and 533/133 mg) twice daily (BID) when given in combination with efavirenz, plus two nucleoside reverse transcriptase inhibitors (not specified), were assessed in a phase II, open-**label**, randomized, parallel arm study in 57 multiple-protease-inhibitor-experienced but non-nucleoside reverse transcriptase inhibitor-naive human **immunodeficiency** virus (HIV)-infected subjects. All the subjects began receiving **lopinavir**/r at 400/100 mg BID; subjects in one arm increased the **lopinavir**/r dose to 533/133 mg BID on day 14. When given in combination with efavirenz, the **lopinavir**/r 400/100 mg BID regimen resulted in lower **lopinavir** concns. in plasma, particularly Cmin, than had been observed in previous studies of **lopinavir**/r administered without efavirenz. Increasing the **lopinavir**/r dose to 533/133 mg increased the **lopinavir** area under the concentration-time curve over a 12-h interval (AUC12), Cpredose, and Cmin by 46, 70, and 141%, resp. The increase in **lopinavir** Cmax (33%,) did not reach statistical significance. Ritonavir AUC12, Cmax, Cpredose, and Cmin values were increased 46-63%. The **lopinavir** predose concns. achieved with the 533/133-mg BID dose were similar to those obtained with **lopinavir**/r at 400/100 mg BID in the absence of efavirenz. Results from univariate logistic regression analyses identified **lopinavir** and efavirenz inhibitory quotient (IQ) parameters, as well as the basal **lopinavir** phenotypic susceptibility, as predictors of antiviral response (HIV RNA <400 copies/mL at week 24); however, no **lopinavir** or efavirenz concentration parameter was identified as a predictor. Multiple stepwise logistic regressions confirmed the significance of the IQ parameters, as well as other basal characteristics, in predicting virol. response after 24 wk in this patient population.

CC 1-5 (Pharmacology)

IT Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(pharmacokinetics and pharmacodynamics of **lopinavir**-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated HIV-infected patients)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 36 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:26944 HCAPLUS
DOCUMENT NUMBER: 138:49361
TITLE: Discrepancies between protease inhibitor concentrations and viral load in reservoirs and sanctuary sites in human immunodeficiency virus-infected patients
AUTHOR(S): Solas, Caroline; Lafeuillade, Alain; Halfon, Philippe; Chadapaud, Stephane; Hittinger, Gilles; Lacarelle, Bruno
CORPORATE SOURCE: Laboratory of Pharmacokinetics, University Hospital,

Marseille, Fr.
SOURCE: Antimicrobial Agents and Chemotherapy (**2003**), 47(1), 238-243
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The variable penetration of antiretroviral drugs into sanctuary sites may contribute to the differential evolution of human **immunodeficiency** virus (HIV) and the emergence of drug resistance. We evaluated the penetration of indinavir, nelfinavir, and **lopinavir**-ritonavir (**lopinavir**/r) in the central nervous system, genital tract, and lymphoid tissue and assessed the correlation with residual viral replication. Plasma, cerebrospinal fluid (CSF), semen, and lymph node biopsy samples were collected from 41 HIV-infected patients on stable highly active antiretroviral therapy regimens to determine drug concns. and HIV RNA levels. When HIV RNA was detectable, sequencing of the reverse transcriptase and protease genes was performed. Ratios of the concentration in semen/concentration in plasma were 1.9 for indinavir, 0.08 for nelfinavir, and 0.07 for **lopinavir**. Only indinavir was detectable in CSF, with a concentration in CSF/concentration in plasma ratio of 0.17. Differential penetration into lymphoid tissue was observed, with concentration in lymph node tissue/concentration in plasma ratios of 2.07, 0.58, and 0.21 for indinavir, nelfinavir, and **lopinavir**, resp. HIV RNA levels were <50 copies/mL in all CSF samples of patients in whom HIV RNA was not detectable in plasma. HIV RNA was detectable in the semen of three patients (two patients receiving nelfinavir and one patient receiving **lopinavir**/r), and its detection was associated with multiple resistance mutations, while the viral load in plasma was undetectable. HIV RNA was detectable in all lymph node tissue samples. Differential drug penetration was observed among the three protease inhibitors in the sanctuary sites, but there was no correlation between drug levels and HIV RNA levels, suggesting that multiple factors are involved in the persistence of viral reservoirs. Further studies are required to clarify the role and clin. relevance of drug penetration in sanctuaries in terms of long-term efficacy and drug resistance.
CC 1-2 (Pharmacology)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 37 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:977321 HCAPLUS
DOCUMENT NUMBER: 139:46441
TITLE: **Immunovirological** outcomes in 70 HIV-1-infected patients who switched to **lopinavir**/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study
AUTHOR(S): Bongiovanni, Marco; Bini, Teresa; Tordato, Federica; Cicconi, Paola; Melzi, Sara; Repetto, Dolores; Sollima, Salvatore; Rusconi, Stefano; Monforte, Antonella d'Arminio
CORPORATE SOURCE: University of Milan, Institute of Infectious and Tropical Diseases, Luigi Sacco Hospital, Milan, 20157, Italy
SOURCE: Journal of Antimicrobial Chemotherapy (**2003**), 51(1), 171-174
CODEN: JACHDX; ISSN: 0305-7453

PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **immunovirol**. outcome of **lopinavir**/ritonavir was evaluated in 70 antiretroviral-experienced HIV patients; at baseline, median CD4+ cell count was 218 cells/mm3 and median plasma viremia 4.58 log10 copies/mL. After 12 mo, we observed an increase in CD4+ cell count to 322 cells/mm3 (P = 0.0001) and a decrease in plasma viremia to 2.35 log10 copies/mL (P = 0.0001). Four patients discontinued **lopinavir** /ritonavir during observation. Among metabolic parameters, only triglyceride concns. increased during treatment (P = 0.02). Twenty-six patients had a genotypic resistance test at baseline; four had ≥6 mutations known to reduce susceptibility to **lopinavir**/ritonavir. Undetectable plasma viremia was obtained only in patients with ≤5 mutations (61.9%).
CC 1-5 (Pharmacology)
Section cross-reference(s): 15
IT Anti-AIDS agents
Antiviral agents
Human
Human **immunodeficiency** virus 1
Multidrug resistance
Viremia
(**immunovirol**. outcomes in 70 HIV-1-infected patients who switched to **lopinavir**/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study)
IT Glycerides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(triglyceride; **immunovirol**. outcomes in 70 HIV-1-infected patients who switched to **lopinavir**/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study)
IT 155213-67-5, Ritonavir 192725-17-0, **Lopinavir**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**immunovirol**. outcomes in 70 HIV-1-infected patients who switched to **lopinavir**/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study)
IT 144114-21-6, HIV protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **immunovirol**. outcomes in 70 HIV-1-infected patients who switched to **lopinavir**/ritonavir after failing at least one protease inhibitor-containing regimen: a retrospective cohort study)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 38 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:973660 HCAPLUS
DOCUMENT NUMBER: 138:32850
TITLE: Analysis of the virological response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving lopinavir/ritonavir therapy
AUTHOR(S): Kempf, Dale J.; Isaacson, Jeffrey D.; King, Martin S.; Brun, Scott C.; Sylte, Jacquelyn; Richards, Bruce; Bernstein, Barry; Rode, Richard; Sun, Eugene
CORPORATE SOURCE: Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, USA

SOURCE: Antiviral Therapy (**2002**), 7(3), 165-174
CODEN: ANTHFA; ISSN: 1359-6535
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The virol. response of multiple protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor-naive, HIV-1-infected subjects was examined with respect to baseline viral phenotype and genotype through 72 wk of therapy with lopinavir/ritonavir plus efavirenz and nucleoside reverse transcriptase inhibitors (Study M98-957). Using a 'dropouts as censored' anal., plasma HIV RNA ≤400 copies/mL was observed in 93% (25/27), 73% (11/15) and 25% (2/8) of subjects with <10-fold, 10- to 40-fold, and >40-fold reduced susceptibility to lopinavir at baseline, resp. In addition, virol. response was observed in 91% (21/23), 71% (15/21) and 33% (2/6) of subjects with baseline lopinavir mutation score of 0-5, 6-7 and ≥8, resp. Through 72 wk, all subjects experiencing virol. failure whose baseline isolates contained six or more protease inhibitor mutations had a common genotypic pattern, with mutations at positions 82, 54 and 10, along with a median of four addnl. mutations in protease. However, an equal number of subjects with a similar genotypic pattern experienced virol. response. Further anal. revealed the baseline phenotypic susceptibility to lopinavir to be an addnl. covariate predicting response in this subset of subjects. In multivariate analyses, baseline susceptibility to lopinavir was associated with response at each time point examined (weeks 24, 48 and 72). These results provide guidance for clin. relevant interpretation of phenotypic and genotypic resistance tests when applied to lopinavir/ritonavir.

CC 1-5 (Pharmacology)

IT Anti-AIDS agents
Genotypes
Human
Human **immunodeficiency** virus 1
Phenotypes
(anal. of virol. response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving **lopinavir**/ritonavir therapy)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 39 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:849442 HCAPLUS
DOCUMENT NUMBER: 137:333133
TITLE: Compositions comprising lopinavir and methods for enhancing the bioavailability of pharmaceutical agents
INVENTOR(S): Everitt, Elizabeth A.; Han, Edward K.; Cherian, Sajeev P.; Kempf, Dale J.; Sham, Hing L.; Ng, Shi-chung
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087585	A1	20021107	WO 2002-US13353	20020429 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2445967	AA	20021107	CA 2002-2445967	20020429 <--
US 2002198160	A1	20021226	US 2002-134931	20020429 <--
EP 1387684	A1	20040211	EP 2002-731543	20020429

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2005511481	T2	20050428	JP 2002-584930	20020429
PRIORITY APPLN. INFO.:			US 2001-367353P P	20010501
			WO 2002-US13353 W	20020429

AB This invention relates to enhancement of the bioavailability of pharmaceutically active agents. In particular, this invention relates to the use of lopinavir, its pharmaceutically acceptable equivalent, and derivs. thereof as P-glycoprotein inhibitors. For example, HCT15 cells (which express P-glycoprotein) were treated with either ritonavir or lopinavir or paclitaxel, a known P-glycoprotein substrate, which was used as a control. A large amount of the ritonavir was rapidly eliminated by the HCT15 cells in 15 min, indicating that ritonavir serves as a substrate for P-glycoprotein, and thus is rapidly effluxed out of the cells. In contrast to ritonavir and paclitaxel, approx. 80% of the lopinavir remained in the HCT15 cells after 60 min. The relatively low efflux of the lopinavir by the cells indicates that in comparison to ritonavir and paclitaxel, lopinavir is not a substrate for P-glycoprotein.

IC ICM A61K031-505
ICS A61K031-426; A61P031-18

CC 1-6 (Pharmacology)
Section cross-reference(s): 63

IT Human **immunodeficiency** virus 1
(combination with agents for treatment of; compns. with enhanced bioavailability containing **lopinavir** as P-glycoprotein inhibitor)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 40 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:828811 HCAPLUS

TITLE: **Lopinavir** measurement in pleural effusion in a human **immunodeficiency** virus type 1-infected patient with Kaposi's Sarcoma

AUTHOR(S): Boffito, Marta; Hoggard, Patrick G.; Back, David J.; Bonora, Stefano; Maiello, Agostino; Lucchini, Anna; Di Perri, Giovanni

CORPORATE SOURCE: Pharmacology Research Laboratories, University of Liverpool, Liverpool, L69 3GF, UK

SOURCE: Antimicrobial Agents and Chemotherapy (**2002**), 46(11), 3684-3685
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal; Letter

LANGUAGE: English

AB Unavailable

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 41 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:817946 HCAPLUS
DOCUMENT NUMBER: 137:332776
TITLE: Genotypic and phenotypic cross-resistance patterns to lopinavir and amprenavir in protease inhibitor-experienced patients with HIV viremia
AUTHOR(S): Paulsen, Denise; Liao, Qiming; Fusco, Gregory; St. Clair, Marty; Shaefer, Mark; Ross, Lisa
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: AIDS Research and Human Retroviruses (**2002**), 18(14), 1011-1019
CODEN: ARHRE7; ISSN: 0889-2229
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Genotypic correlates of reduced phenotypic susceptibility to amprenavir (APV) and lopinavir (LPV) were examined in 271 HIV isolates from 207 protease inhibitor (PI)-experienced subjects. All samples were from LPV-naive subjects; two were from APV-experienced subjects. Using a fold resistance (FR) of <2.5, 179 (66%) were APV susceptible. Using FRs of <2.5 and <10, 107 (39%) and 194 (72%), resp., were LPV susceptible. The I84V mutation was the strongest APV resistance marker in PI-experienced subjects in both univariate and multivariate analyses, with an increased relative incidence (RI) of 6.9 with >2.5 FR. Mutations L10I (RI, 1.7), M46I (RI, 2.3), and L90M (RI, 1.9, but 65% linked with the I84V) were associated with decreased APV susceptibility in the univariate anal. ($p < 0.001$). Mutations L10I, G48V, I54T, I54V, and V82A were significantly associated with decreased LPV susceptibility ($p < 0.001$ for each) and had increased RIs of 2.2, 4.4, 13, 4.6, and 3.2, resp. Decreased susceptibility to LPV (FR, ≥10) was significantly associated with prior exposure to the following PIs: ritonavir (RTV) ($p < 0.001$), saquinavir (SQV) ($p < 0.001$), nelfinavir (NFV) ($p = 0.008$), and indinavir (IDV) ($p = 0.028$). Decreased APV susceptibility (FR, ≥2.5) was significantly associated with prior exposure to RTV ($p = 0.009$), NFV ($p = 0.003$), and IDV ($p = 0.021$) but not with prior SQV ($p = 0.103$). These results suggest that APV and LPV have different cross-resistance mutation patterns that may help determine choice of PI therapy after therapy failure.
CC 1-5 (Pharmacology)
IT Genotypes
Human
Human groups
Human **immunodeficiency** virus 1
Phenotypes
(genotypic and phenotypic cross-resistance patterns to **lopinavir** and amprenavir in protease inhibitor-experienced patients with HIV viremia)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 42 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:767302 HCAPLUS
DOCUMENT NUMBER: 138:170506
TITLE: Novel lopinavir analogs incorporating non-aromatic P-1 side chains - synthesis and structure-activity relationships
AUTHOR(S): Sham, Hing L.; Zhao, Chen; Li, Leping; Betebenner, David A.; Saldivar, Ayda; Vasavanonda, Sudthida; Kempf, Dale J.; Plattner, Jacob J.; Norbeck, Daniel W.
CORPORATE SOURCE: Pharmaceutical Discovery, Abbott Laboratories, Abbott

Park, IL, 60064-6101, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2002**), 12(21), 3101-3103
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:170506
AB The HIV protease inhibitor Lopinavir has a pseudosym. core unit incorporating benzyl groups at both P-1, P-1' positions. A series of analogs incorporating non-aromatic side chains at the P-1 position were synthesized and the structure-activity relationships explored.
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7
IT Human
Human **immunodeficiency** virus
(synthesis and structure-activity relationships of HIV protease inhibitor **lopinavir** analogs)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 43 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:657444 HCAPLUS
DOCUMENT NUMBER: 138:162896
TITLE: Simultaneous determination of indinavir, ritonavir and lopinavir (ABT 378) in human plasma by high-performance liquid chromatography
AUTHOR(S): Ray, John; Pang, Edna; Carey, Dianne
CORPORATE SOURCE: Department of Clinical Pharmacology & Toxicology, Institute of Laboratory Medicine, St. Vincent's Hospital, Sydney, 2010, Australia
SOURCE: Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (**2002**), 775(2), 225-230
CODEN: JCBAAI; ISSN: 1570-0232
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An isocratic reversed-phase high-performance liquid chromatog. method with UV detection at 205 nm has been validated for the determination of indinavir, ritonavir and **lopinavir** (ABT 378) in human plasma. The ritonavir analog A-86093.0 was used as internal standard Good chromatog. separation was achieved using a stainless steel column packed with 5 μm Phenomenex Ph hexyl material operated at 40, and a mobile phase consisting of acetonitrile-10 mM potassium phosphate buffer (50:50, volume/volume). The calibration curve for indinavir was linear over the range of 50 to 1000 μg/l while the ritonavir and **lopinavir** calibration curves were linear over the range of 100 to 15000 μg/l. The lower limit of quantitations for indinavir, ritonavir and **lopinavir** were 50, 100 and 100 μg/l, resp., using 500 μl of human plasma. The validation data showed that the assay is sensitive, specific and reproducible for determination of indinavir, ritonavir and **lopinavir**. This method is being used in a therapeutic drug monitoring service to quantitate these therapeutic agents in patients infected with human **immunodeficiency** virus.
CC 1-1 (Pharmacology)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 44 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:639760 HCAPLUS
DOCUMENT NUMBER: 137:210453
TITLE: Human **immunodeficiency** virus type 1 genotypic and pharmacokinetic determinants of the virological response to **lopinavir** -ritonavir-containing therapy in protease inhibitor-experienced patients
AUTHOR(S): Masquelier, Bernard; Breilh, Dominique; Neau, Didier; Lawson-Ayayi, Sylvie; Lavignolle, Valerie; Ragnaud, Jean-Marie; Dupon, Michel; Morlat, Philippe; Dabis, F.; Fleury, H.
CORPORATE SOURCE: The Groupe d'Epidemiologie Clinique du SIDA en Aquitaine, Laboratoire de Virologie, Hopital Pellegrin, CHU de Bordeaux, Bordeaux, 33076, Fr.
SOURCE: Antimicrobial Agents and Chemotherapy (**2002**), 46(9), 2926-2932
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The response to regimens including **lopinavir**-ritonavir (LPV/r) in patients who have received multiple protease (PR) inhibitors (PI) can be analyzed in terms of human **immunodeficiency** virus type 1 (HIV-1) genotypic and pharmacokinetic (pK) determinants. We studied these factors and the evolution of HIV-1 resistance in response to LPV/r in a prospective study of patients receiving LPV/r under a temporary authorization in Bordeaux, France. HIV-1 PR and reverse transcriptase sequences were determined at baseline LPV/r for all the patients and at month 3 (M3) and M6 in the absence of response to treatment. PK measurements were determined at M1 and M3. Virol. failure (VF) was defined as a plasma viral load ≥400 copies/mL at M3. A multivariate anal. of the predictors of VF, including clin. and biol. characteristics and the treatment history of the patients, was performed. The PR gene sequence at M0, including individual mutations or a previously defined LPV mutation score, and the individual exposure to LPV were also included covariates. Sixty-eight patients were enrolled. Thirty-four percent had a virol. response at M3. An LPV mutation score of >5 mutations, the presence of the PR I54V mutation at baseline, a high number of previous PIs, prior therapy with ritonavir or indinavir, absence of coprescription of efavirenz, and a lower exposure to LPV or lower LPV trough concns. were independently associated with VF on LPV/r. Addnl. PI resistance mutations, including primary mutation I50V, could be selected in patients failing on LPV/r. Genotypic and pK parameters should be used to optimize the virol. response to LPV/r in PI-experienced patients and to avoid further viral evolution.

CC 1-5 (Pharmacology)
IT AIDS (disease)
(Human **immunodeficiency** virus type 1 genotypic and pharmacokinetic determinants of the virol. response to **lopinavir**-ritonavir-containing therapy in protease inhibitor-experienced patients: development of AIDS syndrome)
IT Aging, animal
Sex
(Human **immunodeficiency** virus type 1 genotypic and pharmacokinetic determinants of the virol. response to **lopinavir**-ritonavir-containing therapy in protease inhibitor-experienced patients: factors associated with better virol. response)
IT 127779-20-8, Saquinavir 159989-64-7, Nelfinavir 161814-49-9,

Amprenavir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Human **immunodeficiency** virus type 1 genotypic and pharmacokinetic determinants of the virol. response to **lopinavir**-ritonavir-containing therapy in protease inhibitor-experienced patients)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 45 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:616221 HCAPLUS
TITLE: Comparing the conformational flexibility of HIV-1 inhibitors
AUTHOR(S): James, Julia; Pratt, Jennifer; Schram, Kristin; Parish, Carol
CORPORATE SOURCE: Department of Chemistry, Hobart and William Smith Colleges, Geneva, NY, 14456, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (**2002**), COMP-157. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The human **immunodeficiency** virus (HIV) encodes an aspartyl protease enzyme (HIV-PR) that cleaves viral polyprotein precursors, allowing the maturation of the HIV virus that causes the autoimmune deficiency disease (AIDS). Protease inhibitors occupy the basket-shaped active site, interfering with the functioning of the enzyme and preventing the maturation of the virus. This study will use mol. modeling methods to study the conformational behavior in water of different FDA-approved HIV protease inhibitor drugs such as indinavir, saquinavir, nelfinavir, amprenavir, **lopinavir** and ritonavir to determine the similarities and differences in the way these drugs interact with the protease active site. Conformationally accessible structures will be presented along with a cluster anal. performed to identify major conformational families for each inhibitor.

L19 ANSWER 46 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:580633 HCAPLUS
DOCUMENT NUMBER: 137:149667
TITLE: Kaletra (lopinavir/ritonavir)
AUTHOR(S): Corbett, Amanda H.; Lim, Michael L.; Kashuba, Angela D. M.
CORPORATE SOURCE: School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599-7360, USA
SOURCE: Annals of Pharmacotherapy (**2002**), 36(7/8), 1193-1203
CODEN: APHRER; ISSN: 1060-0280
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The aim was to review the pharmacol., virol., pharmacokinetics, efficacy, safety, and clin. use of lopinavir/ritonavir (Kaletra, Abbott Labs.). English-language MEDLINE and AIDSline searches were performed (1966-July 2001) using lopinavir, ABT-378, and Kaletra as key words. Abstrs. from infectious diseases and HIV scientific meetings were identified. Abbott Labs. provided addnl. published and unpublished information. All

publications, meeting abstrs., and unpublished information were reviewed and relevant items included. In vitro and preclin. studies were included as well as Phase II and III clin. trials. Lopinavir/ritonavir is a fixed-dose protease inhibitor (PI) combination used for the treatment of HIV-1 infection. Lopinavir, the active component of this combination, is extensively metabolized by CYP3A4 and produces low systemic concns. when used alone. Ritonavir potently inhibits CYP3A4 and is used to enhance the systemic exposure of lopinavir. This combination results in lopinavir concns. that greatly exceed those necessary in vitro to inhibit both wild-type and PI-resistant HIV isolates. In clin. trials with antiretroviral naive and experienced patients, lopinavir/ritonavir was effective at suppressing HIV-RNA and increasing CD4+ T cell counts. Compared with other PIs, lopinavir/ritonavir may have advantages in the areas of pharmacokinetics, efficacy, and resistance. Toxicity, drug interactions, and medication adherence are important considerations surrounding its clin. use. Lopinavir/ritonavir is an effective option for the treatment of HIV-1-infected individuals when used in combination with other antiretroviral agents. It may be used as a component of initial therapy or salvage therapy; future studies will better define its place in therapy.

CC 1-0 (Pharmacology)

IT Human **immunodeficiency** virus 1
(infection; Kaletra (**lopinavir**/ritonavir) for treatment of HIV-1 infection)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 47 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:501504 HCAPLUS

DOCUMENT NUMBER: 138:66212

TITLE: In vitro antiviral interaction of lopinavir with other protease inhibitors

AUTHOR(S): Molla, Akhteruzzaman; Mo, Hongmei; Vasavanonda, Sudthida; Han, Lixin; Lin, C. Thomas; Hsu, Ann; Kempf, Dale J.

CORPORATE SOURCE: Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, 60064-6217, USA

SOURCE: Antimicrobial Agents and Chemotherapy (**2002**), 46(7), 2249-2253
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The in vitro inhibition of wild-type human **immunodeficiency** virus (HIV) by combinations of **lopinavir** and six other protease inhibitors over a range of two-drug combination ratios was evaluated. Combinations of **lopinavir** with indinavir, nelfinavir, amprenavir, tipranavir, and BMS-232632 generally displayed an additive relationship. In contrast, a consistent, statistically significant synergistic inhibition of HIV type 1 replication with combinations of **lopinavir** and saquinavir was observed Anal. of the combination indexes indicated that **lopinavir** with saquinavir was synergistic over the entire range of drug combination ratios tested and at all levels of inhibition in excess of 40%. Cellular toxicity was not observed at the highest drug concns. tested. These results suggest that administration of combinations of the appropriate dose of **lopinavir** with other protease inhibitors in vivo may result in enhanced antiviral activity with no associated increase in cellular cytotoxicity. More importantly, the observed

in vitro synergy between **lopinavir** and saquinavir provides a theor. basis for the clin. exploration of a novel regimen of **lopinavir**-ritonavir and saquinavir.

CC 1-5 (Pharmacology)
Section cross-reference(s): 10

IT Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(in vitro antiviral interaction of **lopinavir** with other protease inhibitors)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 48 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:492873 HCAPLUS
DOCUMENT NUMBER: 137:119104
TITLE: Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection
AUTHOR(S): Walmsley, Sharon; Bernstein, Barry; King, Martin; Arribas, Jose; Beall, Gildon; Ruane, Peter; Johnson, Margaret; Johnson, David; Lalonde, Richard; Japour, Anthony; Brun, Scott; Sun, Eugene; Allworth, A. M.; Altice, F. L.; Arasteh, K.; Badley, A. D.; Barros, C.; Beal, J.; Brand, J. D.; Cameron, W.; Cimoch, P. J.; Clotet Sala, B.; Cohen, C. J.; Cooley, T. P.; Delfraissy, J.-F.; Faetkenheuer, G.; Farthing, C. F.; Feinberg, J.; Fischl, M. A.; Fisher, M.; Flepp, M.; Gallant, J.; Gathe, J. C.; Gerstoft, J.; Goldman, M.; Gonzalez-Lahoz, J. M.; Graziano, F. M.; Green, S.; Grossman, H. A.; Haas, D. W.; Haas, F. F.; Hauptman, S. P.; Hicks, C. B.; Horban, A.; Horton, J. M.; Hyslop, N. E., Jr.; Kalayjian, R. C.; Kazanjian, P. H.; Kostman, J.; Lampiris, H. W.; LaPlante, F.; Lennox, J. L.; Luskin-Hawk, R.; Mallal, S.; Mathiesen, L.; Silva de Mendonca, J.; Miao, P.; Mildvan, D.; Miller, S.; Montaner, J. S. G.; Mouton, Y.; Myers, R. A., Jr.; Pavia, A. T.; Pedersen, C.; Pierone, G., Jr.; Pollard, R. B.; Pozniak, A.; Rachlis, A. R.; Rhame, F. S.; Rubio, R.; Saimot, A. G.; Sampson, J. H.; Sanne, I.; Santana, J. L.; Seekins, D.; Sepulveda, G. E.; Sereni, D.; Sharma, S.; Sherer, R. D., Jr.; Smith, L. G.; Squires, K. E.; Staszewski, S.; Steigbigel, R. T.; Steinhart, C. R.; Stoehr, A.; Stryker, R.; Sweet, D. E.; Tashima, K. T.; Theisen, A.; Thomas, R.; Thommes, J. A.; Thompson, M. A.; Timermann, A.; Viciana, P.; Vittecoq, D.; Weber, J. N.; Weitner, D. L.; van der Westhuizen, I. P.; Wheeler, D. A.; Wright, D. P.; Yangco, B. G.
CORPORATE SOURCE: M98-863 Study Team, Toronto Hospital, Univ. Health Network, University Toronto, Toronto, ON, Can.
SOURCE: New England Journal of Medicine (**2002**), 346(26), 2039-2046
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Lopinavir** is a newly developed inhibitor of human **immunodeficiency** virus (HIV) protease that, when formulated with ritonavir, yields mean trough plasma **lopinavir** concns. that are

at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50 %. We conducted a double-blind trial in which 653 HIV-infected adults who had not received anti-retroviral therapy for more than 14 days were randomly assigned to receive either **lopinavir** -ritonavir (400 mg of **lopinavir** plus 100 mg of ritonavir twice daily) with nelfinavir placebo or nelfinavir (750 mg three times daily) with **lopinavir**-ritonavir placebo. All patients also received open-**label** stavudine and lamivudine. The primary efficacy end points were the presence of fewer than 400 HIV RNA copies per mL of plasma at week 24 and the time to the loss of virol. response through week 48. At week 48, greater proportions of patients treated with **lopinavir** -ritonavir than of patients treated with nelfinavir had fewer than 400 copies of HIV RNA per mL (75 % vs. 63 %, P < 0.001) and fewer than 50 copies per mL (67 % vs. 52 %, P < 0.001). The time to the loss of virol. response was greater in the **lopinavir**-ritonavir group than in the nelfinavir group (hazard ratio, 2.0; 95 % confidence interval, 1.5 to 2.7; P < 0.001). The estimated proportion of patients with a persistent virol. response through week 48 was 84 % for patients receiving **lopinavir**-ritonavir and 66 % for those receiving nelfinavir. Both regimens were well tolerated, with the rate of discontinuation related to the study drugs at 3.4 % among patients receiving **lopinavir** -ritonavir and 3.7 % among patients receiving nelfinavir. Among patients with more than 400 copies of HIV RNA per mL at some point from week 24 through week 48, resistance mutations in HIV protease were demonstrated in viral isolates from 25 to 76 nelfinavir-treated patients (33 %) and none of 37 patients treated with **lopinavir**-ritonavir (P < 0.001). For the initial treatment of HIV-infected adults, a combination regimen that includes **lopinavir**-ritonavir is well tolerated and has antiviral activity superior to that of a nelfinavir-containing regimen.

CC 1-5 (Pharmacology)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 49 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:476090 HCAPLUS
DOCUMENT NUMBER: 138:82710
TITLE: New developments in anti-HIV chemotherapy
AUTHOR(S): De Clercq, Erik
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Biochimica et Biophysica Acta, Molecular Basis of Disease (**2002**), 1587(2-3), 258-275
CODEN: BBADEX; ISSN: 0925-4439
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Virtually all the compds. that are currently used, or are subject of advanced clin. trials, for the treatment of human **immunodeficiency** virus (HIV) infections, belong to one of the following classes: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs): i.e. zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir (ABC), emtricitabine [(-)FTC], tenofovir disoproxil fumarate; (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs): i.e. nevirapine, delavirdine, efavirenz, emivirine; and (iii) protease inhibitors (PIs): i.e. saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and **lopinavir**. In addition to the reverse transcriptase (RT) and protease reaction, various other events in the HIV replicative cycle can be considered as potential targets for chemotherapeutic intervention: (i)

viral adsorption, through binding to the viral envelope glycoprotein gp120 (polysulfates, polysulfonates, polycarboxylates, polyoxometalates, polynucleotides, and neg. charged albumins); (ii) viral entry, through blockade of the viral coreceptors CXCR4 [bicyclam (AMD3100) derivs.] and CCR5 (TAK-779 derivs.); (iii) virus-cell fusion, through binding to the viral envelope glycoprotein gp41 (T-20, T-1249); (iv) viral assembly and disassembly, through NCp7 zinc finger-targeted agents [2,2'-dithiobisbenzamides (DIBAs), azadicarbonamide (ADA)]; (v) proviral DNA integration, through integrase inhibitors such as 4-aryl-2,4-dioxobutanoic acid derivs.; (vi) viral mRNA transcription, through inhibitors of the transcription (transactivation) process (flavopiridol, fluoroquinolones). Also, various new NRTIs, NNRTIs and PIs have been developed that possess, resp.: (i) improved metabolic characteristics (i.e. phosphoramidate and cyclosaligenyl pronucleotides by-passing the first phosphorylation step of the NRTIs), (ii) increased activity ["second" or "third" generation NNRTIs (i.e. TMC-125, DPC-083)] against those HIV strains that are resistant to the "first" generation NNRTIs, or (iii) as in the case of PIs, a different, nonpeptidic scaffold [i.e. cyclic urea (mozenavir), 4-hydroxy-2-pyrone (tipranavir)]. Nonpeptidic PIs may be expected to inhibit HIV mutant strains that have become resistant to peptidomimetic PIs. Given the multitude of mol. targets with which anti-HIV agents can interact, one should be cautious in extrapolating the mode of action of these agents from cell-free enzymic assays to intact cells. Two examples in point are l-chicoric acid and the nonapeptoid CGP64222, which were initially described as an integrase inhibitor or Tat antagonist, resp., but later shown to primarily act as virus adsorption/entry inhibitors, the latter through blockade of CXCR4.

CC 1-0 (Pharmacology)

REFERENCE COUNT: 148 THERE ARE 148 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 50 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:465502 HCAPLUS

DOCUMENT NUMBER: 138:49317

TITLE: ~~High-performance liquid chromatographic method~~ for the simultaneous determination of the six HIV-protease inhibitors and two non-nucleoside reverse transcriptase inhibitors in human plasma

AUTHOR(S): Titier, Karine; Lagrange, Fabrice; Pehourcq, Fabienne; Edno-Mcheik, Leila; Moore, Nicholas; Molimard, Mathieu

CORPORATE SOURCE: Department of Clinical Pharmacology and Toxicology, Pellegrin Hospital and University Victor Segalen, Bordeaux, 33076, Fr.

SOURCE: Therapeutic Drug Monitoring (**2002**), 24(3), 417-424
CODEN: TDMODV; ISSN: 0163-4356

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A selective and sensitive high-performance liquid chromatog. (HPLC) method was developed for the determination of the 6 human **immunodeficiency** virus (HIV)-protease inhibitors (amprenavir, indinavir, **lopinavir** , nelfinavir, ritonavir, and saquinavir) and the non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) in a single run. After a liquid-liquid extraction with di-Et ether, the 6 protease inhibitors and the 2 non-nucleoside reverse transcriptase inhibitors are separated on a Stability RP18 column eluted with a gradient of acetonitrile and phosphate

buffer 50 mmol/L pH 5.65. A sequential UV detection (5-min sequence set at 240 nm for nevirapine acquisition, 22-min sequence set at 215 nm for other antiretroviral drugs acquisition followed by a sequence set at 260 nm for internal standard acquisition) allowed for simultaneous quantitation of the 6 protease inhibitors, nevirapine, and efavirenz. Calibration curves were linear in the range 100 ng/mL to 10,000 ng/mL. The limit of quantitation was 50 ng/mL for all drugs except nevirapine (100 ng/mL). Average accuracy at 4 concns. ranged from 88.2 to 110.9%. Both interday and intraday coeffs. of variation were < 11% for all drugs. The extraction recoveries were greater than 62%. This method is simple and shows a good specificity with respect to commonly co-prescribed drugs. This method allows accurate therapeutic monitoring of amprenavir, indinavir, **lopinavir**, nelfinavir, ritonavir, saquinavir, efavirenz, and nevirapine.

CC 1-1 (Pharmacology)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 51 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:441654 HCAPLUS

DOCUMENT NUMBER: 137:362559

TITLE: Select HIV protease inhibitors alter bone and fat metabolism ex vivo

AUTHOR(S): Jain, Renu G.; Lenhard, James M.

CORPORATE SOURCE: Department of Metabolic Diseases, GlaxoSmithKline Inc., Research Triangle Park, NC, 27709, USA

SOURCE: Journal of Biological Chemistry (**2002**), 277(22), 19247-19250
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human **immunodeficiency** virus (HIV) therapies have been associated with alterations in fat metabolism and bone mineral d. This study examined the effects of HIV protease inhibitors (PIs) on bone resorption, bone formation, and adipocyte differentiation using ex vivo cultured osteoclasts, osteoblasts, and adipocytes, resp. Osteoclast activity, measured using a rat neonatal calvaria assay, increased in the presence of nelfinavir (NFV; 47.2%, p = 0.001), indinavir (34.6%, p = 0.001), saquinavir (24.3%, p = 0.001), or ritonavir (18%, p < 0.01). In contrast, **lopinavir** (LPV) and amprenavir did not increase osteoclast activity. In human mesenchymal stem cells (hMSCs), the PIs LPV and NFV decreased osteoblast alkaline phosphatase enzyme activity and gene expression significantly (p < 0.05). LPV and NFV diminished calcium deposition and osteoprotegerin expression (p < 0.05), whereas the other PIs investigated did not. Adipogenesis of hMSCs was strongly inhibited by saquinavir and NFV (>50%, p < 0.001) and moderately inhibited by ritonavir and LPV (>40%, p < 0.01). Expression of diacylglycerol transferase, a marker of adipocyte differentiation, decreased in hMSCs treated with NFV. Amprenavir and indinavir did not affect adipogenesis or lipolysis. These results suggest that bone and fat formation in hMSCs of bone marrow may be coordinately down-regulated by some but not all PIs.

CC 1-5 (Pharmacology)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 52 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:437414 HCAPLUS

DOCUMENT NUMBER: 138:66196
TITLE: Amprenavir-resistant HIV-1 exhibits lopinavir cross-resistance and reduced replication capacity
AUTHOR(S): Prado, Julia G.; Wrin, Terri; Beauchaine, Jeff; Ruiz, Lidia; Petropoulos, Christos J.; Frost, Simon D. W.; Clotet, Bonaventura; D'Aquila, Richard T.; Martinez-Picado, Javier
CORPORATE SOURCE: IrsiCaixa Foundation, Hospital Germans Trias i Pujol, Universitat Autonoma de Barcelona, Badalona, Spain
SOURCE: AIDS (London, United Kingdom) (**2002**), 16(7), 1009-1017
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To evaluate protease inhibitor (PI) cross-resistance and redns. in replication capacity conferred by amprenavir-selected mutations. HIV-1IIIB variants derived from passage in increasing concns. of amprenavir were studied, as well as 3'Gag/protease recombinants derived from them. These strains progressively accumulated mutations at codons 10, 46, 47, 50 and 84 in the protease as well as a p1/p6 cleavage site mutation at codon 449 in Gag. Their susceptibility (IC50) to various PI and their corresponding replication capacities were evaluated by a single-cycle growth assay and compared with measures using competitive cultures and p24 **antigen** production Amprenavir susceptibility decreased with increasing nos. of protease mutations. Changes in **lopinavir** susceptibility paralleled changes in amprenavir susceptibility. Certain amprenavir-selected mutants conferred greater than 10-fold cross-resistance to **lopinavir**, including PrL10F/M46I/I50V-GagL449F (19-fold) and PrL10F/M46I/I47V/I50V-GagL449F (31-fold). Moreover, one isolate with only two mutations in the protease (L10F/84V) and GagL449F displayed a 7.7-fold increase in **lopinavir** IC50. Low-level cross-resistance to ritonavir and nelfinavir was also observed The replication capacity of viruses containing either I84V or I50V was at least 90% lower than the reference virus in the single-cycle assay. The order of relative replication capacity was wild-type > L10F > L10F/I84V > L10F/M46I/I50V > L10F/M46I/I47V/I50V. These results indicate that until more comprehensive genotype-phenotype correlations between amprenavir and **lopinavir** susceptibility are established, phenotypic testing may be preferable to genotyping to detect cross-resistance, and should be considered when switching patients from a failing amprenavir-containing regimen. This study also provides data on the concordance of replication capacity measurements generated using rapid single-cycle growth and competition assays.

CC 1-5 (Pharmacology)
IT Human **immunodeficiency** virus 1
(variants; amprenavir-resistant HIV-1 exhibits **lopinavir** cross-resistance and reduced replication capacity)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 53 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:358148 HCAPLUS
DOCUMENT NUMBER: 137:206
TITLE: Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir-ritonavir
AUTHOR(S): Clarke, Susan; Mulcahy, Fiona; Begin, Colm; Reynolds,

Helen; Boyle, Nicola; Barry, Michael; Back, David J.
CORPORATE SOURCE: Genitourinary Medicine and Infectious Disease Clinic, Liverpool, UK
SOURCE: Clinical Infectious Diseases (**2002**), 34(8), 1143-1145
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was designated to determine the interactions, both clin. and pharmacokinetic, between methadone and lopinavir-ritonavir. Results demonstrated a 36% reduction in the methadone area under the plasma concentration-time curve after the introduction of lopinavir-ritonavir, with no coincident symptoms of opioid withdrawal and no requirement for methadone dose adjustment.
CC 1-4 (Pharmacology)
IT AIDS (disease)
Anti-AIDS agents
Drug withdrawal
Human
Human **immunodeficiency** virus 1
(pharmacokinetic interaction and absence of opioid withdrawal symptoms in humans receiving methadone and protease inhibitor **lopinavir** -ritonavir)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 54 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:334512 HCAPLUS
DOCUMENT NUMBER: 137:333620
TITLE: Rapid and sensitive oligonucleotide ligation assay for detection of mutations in human immunodeficiency virus type 1 associated with high-level resistance to protease inhibitors
AUTHOR(S): Beck, Ingrid A.; Mahalanabis, Madhumita; Pepper, Gregory; Wright, Amy; Hamilton, Shannon; Langston, Erika; Frenkel, Lisa M.
CORPORATE SOURCE: Departments of Pediatrics, University of Washington, Seattle, WA, USA
SOURCE: Journal of Clinical Microbiology (**2002**), 40(4), 1413-1419
CODEN: JCMIDW; ISSN: 0095-1137
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive, specific, and high-throughput oligonucleotide ligation assay (OLA) for the detection of genotypic human **immunodeficiency** virus type 1 (HIV-1) resistance to Food and Drug Administration-approved protease inhibitors was developed and evaluated. This ligation-based assay uses differentially modified oligonucleotides specific for wild-type or mutant sequences, allowing sensitive and simple detection of both genotypes in a single well of a microtiter plate. Oligonucleotides were designed to detect primary mutations associated with high-level resistance to amprenavir, nelfinavir, indinavir, ritonavir, saquinavir, and **lopinavir**, including amino acid substitutions D30N, I50V, V82A/S/T, I84V, N88D, and L90M. Plasma HIV-1 RNA from 54 infected patients was amplified by reverse transcription-PCR and sequenced by using dideoxynucleotide chain terminators for evaluation of mutations associated with drug resistance. These same amplicons were genotyped by the OLA at

positions 30, 50, 82, 88, 84, and 90 for a total of 312 codons. The sensitivity of detection of drug-resistant genotypes was 96.7% (87 of 90 mutant codons) in the OLA compared to 92.2% (83 of 90) in consensus sequencing, presumably due to the increased sensitivity of the OLA. The OLA detected genetic subpopulations more often than sequencing, detecting 30 mixts. of mutant and wild-type sequences and two mixts. of drug-resistant sequences compared to 15 detected by DNA sequencing. Reproducible and semiquant. detection of the mutant and the wild-type genomes by the OLA was observed by anal. of wild-type and mutant plasmid mixts. containing as little as 5% of either genotype in a background of the opposite genome. This rapid, simple, economical, and highly sensitive assay provides a practical alternative to dideoxy sequencing for genotypic evaluation of HIV-1 resistance to antiretrovirals.

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 1

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid and sensitive oligonucleotide ligation assay for detection of mutations in human **immunodeficiency** virus type 1 protease associated with high-level resistance to protease inhibitors)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 55 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:255564 HCAPLUS
DOCUMENT NUMBER: 137:241546
TITLE: Lopinavir/ritonavir (ABT-378/r)
AUTHOR(S): Qazi, Nadeem A.; Morlese, John F.; Pozniak, Anton L.
CORPORATE SOURCE: St. Stephen's Centre, Department of HIV/GUM, Chelsea and Westminster Hospital, London, UK
SOURCE: Expert Opinion on Pharmacotherapy (**2002**), 3(3), 315-327
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Despite major advances in HIV research, eradication of HIV from the body is not yet possible. However, current antiretroviral (ARV) therapy can achieve disease control via viral suppression below the limits of detection of currently available assays. This has led to a marked decline in morbidity and mortality associated with the development of opportunistic infections and malignancies. Since viral suppression appears to be the most achievable goal of current therapy, there arises a need for new and more potent ARV agents in order to maintain viral suppression. Many of the currently available protease inhibitors (Pls) have a high protein-binding ability, short plasma half-life and pharmacokinetic interactions with food or other drugs. This can result in sub-optimal plasma drug concns., which may allow the virus to break through and replicate, leading to the development of resistant mutants. Lopinavir/ritonavir (LPV/r; Kaletra, Abbott Labs.) is a new Pl consisting of a co-formulation of lopinavir and low-dose ritonavir. The sub-therapeutic dose of ritonavir (a potent cytochrome P 450 [CYP] 3A4 inhibitor) inhibits the metabolism of lopinavir, resulting in higher lopinavir concns. than when lopinavir is administered alone. This pharmacokinetic interaction is associated with a high lopinavir trough level:wild type median effective concentration (EC50) ratio and good general tolerability when compared

with other currently licensed Pls. The concept of pharmacokinetic enhancement - boosting - is not new as ritonavir has previously been utilized in this context with other Pls. The relationship between plasma and intracellular drug levels has yet to be clarified. What has been ascertained from pharmacokinetic studies thus far is the correlation between ARV trough plasma concns. (Cmin) and virol. outcome. LPV/r exemplifies how the pharmacokinetic profile of a drug can be modified to attain sufficient Cmin to suppress pheno- and genotypically resistant viral strains, as well as provide a pharmacol. barrier to the emergence of resistance. LPV/r reduces pillburden and aids compliance, as shown by encouraging results in the treatment of both ARV-naive and -experienced patients.

CC 1-0 (Pharmacology)

IT AIDS (disease)
Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(**lopinavir**/ritonavir (ABT-378/r) in treatment of HIV)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 56 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:251345 HCAPLUS
DOCUMENT NUMBER: 137:288475
TITLE: Synthesis and structure-activity relationships of a novel series of HIV-1 protease inhibitors encompassing ABT-378 (Lopinavir)
AUTHOR(S): Sham, Hing L.; Betebenner, David A.; Chen, Xiaoqi; Saldivar, Ayda; Vasavanonda, Sudthida; Kempf, Dale J.; Plattner, Jacob J.; Norbeck, Daniel W.
CORPORATE SOURCE: Abbott Laboratories, Pharmaceutical Discovery, Abbott Park, IL, 60064-6101, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2002**), 12(8), 1185-1187
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:288475

AB The HIV protease inhibitor ABT-378 (Lopinavir) has a 2,6-dimethylphenoxyacetyl group in the P-2' position. Analogs in which this group is replaced with various substituted Ph or heteroaryl groups were synthesized and the structure-activity relationships explored.

CC 1-3 (Pharmacology)
Section cross-reference(s): 34

IT Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
Lipophilicity
(synthesis and structure-activity relationships of a novel series of HIV-1 protease inhibitors encompassing ABT-378 (**Lopinavir**))

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 57 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:223196 HCAPLUS
DOCUMENT NUMBER: 136:379516
TITLE: Safety and antiviral activity at 48 weeks of **lopinavir**/ritonavir plus nevirapine and 2

nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected protease inhibitor-experienced patients

AUTHOR(S): Benson, Constance A.; Deeks, Steven G.; Brun, Scott C.; Gulick, Roy M.; Eron, Joseph J.; Kessler, Harold A.; Murphy, Robert L.; Hicks, Charles; King, Martin; Wheeler, David; Feinberg, Judith; Stryker, Richard; Sax, Paul E.; Riddler, Sharon; Thompson, Melanie; Real, Kathryn; Hsu, Ann; Kempf, Dale; Japour, Anthony J.; Sun, Eugene

CORPORATE SOURCE: Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SOURCE: Journal of Infectious Diseases (**2002**), 185(5), 599-607
CODEN: JIDIAQ; ISSN: 0022-1899

PUBLISHER: University of Chicago Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The safety and antiviral activity of **lopinavir** (Lpv), a protease inhibitor (PI) coformulated with ritonavir (Rtv) to enhance its pharmacokinetic properties, were evaluated in 70 patients with plasma human **immunodeficiency** virus type 1 (HIV-1) RNA levels of 1000-100,000 copies/mL on a first PI-containing regimen. Patients were randomized to substitute only the PI with Lpv/Rtv, 400/100 mg or 400/200 mg twice daily. On day 15, nevirapine (200 mg 2+/day) was added, and nucleoside reverse-transcriptase inhibitors were changed. Despite a >4-fold reduction in phenotypic susceptibility to the preentry PI in 63% of patients, mean plasma HIV-1 RNA levels declined by 1.14 log10 copies/mL after 2 wk of Lpv/Rtv. At week 48, 86% of subjects receiving treatment had plasma HIV-1 RNA levels of <400 copies/mL; 76% had levels <50 HIV-1 RNA copies/mL (intent-to-treat: 70% and 60%, resp.). Mean CD4 cell counts increased by 125 cells/μL. Three patients discontinued therapy for drug-related adverse events.

CC 1-5 (Pharmacology)

IT Drug resistance
(antiviral; safety and antiviral activity at 48 wk of **lopinavir** /ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected protease inhibitor-experienced patients)

IT Anti-AIDS agents
Human
Human **immunodeficiency** virus 1
(safety and antiviral activity at 48 wk of **lopinavir** /ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected protease inhibitor-experienced patients)

IT 9068-38-6, Reverse transcriptase 144114-21-6, Hiv protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; safety and antiviral activity at 48 wk of **lopinavir** /ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected protease inhibitor-experienced patients)

IT 369372-47-4
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and antiviral activity at 48 wk of **lopinavir** /ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected

protease inhibitor-experienced patients)
IT 129618-40-2, Nevirapine 155213-67-5, Ritonavir 192725-17-0, **Lopinavir**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and antiviral activity at 48 wk of **lopinavir** /ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in human **immunodeficiency** virus type 1-infected protease inhibitor-experienced patients)
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 58 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:172806 HCAPLUS
DOCUMENT NUMBER: 136:303484
TITLE: Efficacy of highly active antiretroviral therapy in HIV-1 infected children
AUTHOR(S): Van Rossum, Annemarie M. C.; Fraaij, Pieter L. A.; De Groot, Ronald
CORPORATE SOURCE: Sophia Children's Hospital, Rotterdam, 3015 GJ, Neth.
SOURCE: Lancet Infectious Diseases (**2002**), 2(2), 93-102
CODEN: LIDABP; ISSN: 1473-3099
PUBLISHER: Lancet Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Although the reduction in HIV-1-related deaths with highly active antiretroviral therapy (HAART) is similar in adults and children, the extent of the changes in two important surrogate markers HIV-1 RNA levels and CD4+ T cell counts, differs widely. In most pediatric studies virol. response rates to HAART are inferior to those in adults. This review provides an overview of the pediatric clin. studies using HAART and seeks to improve the understanding of factors that may contribute to success or failure of HAART in children. An overview of all current articles on pediatric clin. trials using HAART is provided, 23 papers were available. HIV-1 RNA loads and CD4+ T cell counts were used as primary outcome measures. Virol. response rates were highly variable, both among the different antiretroviral drugs but also among different studies using the same medication. Four studies in which dosages of the administered protease inhibitor (PI) were adjusted after pharmacokinetic evaluation had superior virol. response rates compared with those in which fixed dosages were used. **Immunol**. response rates were more uniform than virol. responses. In almost all studies increases of CD4+ T cell counts are reported independent of the extent of the virol. response. Side-effects of HAART were generally mild, transient, and of gastrointestinal origin. Significant percentages of patients with serum lipid abnormalities were reported in three pediatric studies. However, signs of clin. lipodystrophy were not observed The inferior virol. response rates, which have been reported in HIV-1 infected children treated with HAART form a reflection of the challenges that are encountered in the treatment of these children. Difficulties with adherence and with the pharmacokinetics of PIs in children require an intensive, child-adjusted approach. A practical approach to therapy in institutions without tertiary care facilities may be induction therapy with a **lopinavir** containing regimen (lacking a need for therapeutic drug monitoring), to reduce high viral load levels followed by an easily tolerated maintenance regimen, for example containing abacavir or nevirapine.
CC 1-0 (Pharmacology)
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 59 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:74803 HCAPLUS
DOCUMENT NUMBER: 136:272626
TITLE: Pharmacokinetics of amprenavir and lopinavir in combination with nevirapine in highly pretreated HIV-infected patients
AUTHOR(S): Fatkenheuer, Gerd; Roemer, Katja; Kamps, Robert; Salzberger, Bernd; Burger, David
CORPORATE SOURCE: UK
SOURCE: AIDS (London, United Kingdom) (**2001**), 15(17), 2334-2335
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A pharmacokinetic study was performed in five patients treated with the combination of amprenavir, lopinavir and nevirapine. Although the concns. of amprenavir were within the expected range, lopinavir concns. varied widely and tended to be lower than predicted by the manufacturer. We concluded that therapeutic drug monitoring should be performed when this combination is applied.
CC 1-2 (Pharmacology)
IT Anti-AIDS agents
CD4-positive T cell
Human
Human **immunodeficiency** virus 1
(pharmacokinetics of amprenavir and **lopinavir** in combination with nevirapine in highly pretreated HIV-infected patients)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 60 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:903574 HCAPLUS
DOCUMENT NUMBER: 136:160777
TITLE: Lopinavir-ritonavir: A new protease inhibitor
AUTHOR(S): Mangum, Eric M.; Graham, Kathleen K.
CORPORATE SOURCE: Department of Pharmacy Practice, College of Pharmacy, Nova Southeastern University, Ft. Lauderdale, FL, USA
SOURCE: Pharmacotherapy (**2001**), 21(11), 1352-1363
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. **Lopinavir** is a new protease inhibitor that is structurally related to ritonavir. It recently was approved by the Food and Drug Administration as a coformulation with ritonavir under the brand name Kaletra. Ritonavir substantially increases **lopinavir** drug exposure by inhibiting cytochrome P 450 isoenzyme 3A4. Based on limited data, **lopinavir**-ritonavir demonstrates safety and efficacy in both antiretroviral-naive and protease inhibitor-experienced patients. It has the ability to durably suppress human **immunodeficiency** virus (HIV) RNA for up to 2 yr in antiretroviral-naive patients. Compared with nelfinavir, it had superior virol. control at 48 wk in antiretroviral-naive patients. Its side effects include diarrhea, abnormal stools, abdominal pain, nausea, vomiting, and asthenia. A number of patients experienced grade 3-4 laboratory abnormalities in liver function tests,

cholesterol, and triglycerides while receiving this drug combination. The exact resistance patterns of **lopinavir**-ritonavir are unknown, but the Department of Health and Human Services strongly recommends it for the initial treatment of HIV-infected adults and adolescents.
CC 1-0 (Pharmacology)
IT Antiviral agents
Human
Human **immunodeficiency** virus 1
(**lopinavir**-ritonavir combination (Kaletra): new protease inhibitor for HIV-infected humans)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 61 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:561862 HCAPLUS
DOCUMENT NUMBER: 135:313220
TITLE: Antiretroviral therapy effects on genetic and morphologic end points in lymphocytes and sperm of men with human immunodeficiency virus infection
AUTHOR(S): Robbins, Wendie A.; Witt, Kristine L.; Haseman, Joseph K.; Dunson, David B.; Troiani, Luigi; Cohen, Myron S.; Hamilton, Carol D.; Perreault, Sally D.; Libbus, Bishara; Beyler, Stan A.; Raburn, Douglas J.; Tedder, Shelia T.; Shelby, Michael D.; Bishop, Jack B.
CORPORATE SOURCE: Laboratory of Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709, USA
SOURCE: Journal of Infectious Diseases (**2001**), 184(2), 127-135
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Many human immunodeficiency virus (HIV)-infected persons receive prolonged treatment with DNA-reactive antiretroviral drugs. A prospective study was conducted of 26 HIV-infected men who provided samples before treatment and at multiple times after beginning treatment, to investigate effects of antiretrovirals on lymphocyte and sperm chromosomes and semen quality. Several antiretroviral regimens, all including a nucleoside component, were used. Lymphocyte metaphase anal. and sperm fluorescence in situ hybridization were used for cytogenetic studies. Semen analyses included conventional parameters (volume, concentration, viability, motility and morphol.).
No significant effects on cytogenetic parameters, semen volume, or sperm concentration were detected. However, there were significant improvements in sperm motility for men with study entry CD4 cell counts>200 cells/mm3, sperm morphol. for men with entry CD4 cell counts ≤200 cells/mm3, and the percentage of viable sperm in both groups. These findings suggest that nucleoside-containing antiretrovirals administered via recommended protocols do not induce chromosomal changes in lymphocytes or sperm but may produce improvements in semen quality.
CC 1-5 (Pharmacology)
IT 3056-17-5, Stavudine 30516-87-1, Zidovudine 134678-17-4, Lamivudine 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, **Lopinavir**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiretroviral therapy effects on genetic and morphol. end points in

lymphocytes and sperm of men with human **immunodeficiency** virus infection)
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 62 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:556787 HCAPLUS
DOCUMENT NUMBER: 135:285560
TITLE: Identification of genotypic changes in human **immunodeficiency** virus protease that correlate with reduced susceptibility to the protease inhibitor **lopinavir** among viral isolates from protease inhibitor-experienced patients
AUTHOR(S): Kempf, Dale J.; Isaacson, Jeffrey D.; King, Martin S.; Brun, Scott C.; Xu, Yi; Real, Kathryn; Bernstein, Barry M.; Japour, Anthony J.; Sun, Eugene; Rode, Richard A.
CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Journal of Virology (**2001**), 75(16), 7462-7469
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The association of genotypic changes in human **immunodeficiency** virus (HIV) protease with reduced in vitro susceptibility to the new protease inhibitor **lopinavir** (previously ABT-378) was explored using a panel of viral isolates from subjects failing therapy with other protease inhibitors. Two statistical tests showed that specific mutations at 11 amino acid positions in protease (L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M) were associated with reduced susceptibility. Mutations at positions 82, 54, 10, 63, 71, and 84 were most closely associated with relatively modest (4- and 10-fold) changes in phenotype, while the K20M/R and F53L mutations, in conjunction with multiple other mutations, were associated with >20- and >40-fold-reduced susceptibility, resp. The median 50% inhibitory concns. (IC50) of **lopinavir** against isolates with 0 to 3, 4 or 5, 6 or 7, and 8 to 10 of the above 11 mutations were 0.8-, 2.7-, 13.5-, and 44.0-fold higher, resp., than the IC50 against wild-type HIV. On average, the IC50 of **lopinavir** increased by 1.74-fold per mutation in isolates containing three or more mutations. Each of the 16 viruses that displayed a >20-fold change in susceptibility contained mutations at residues 10, 54, 63, and 82 and/or 84, along with a median of three mutations at residues 20, 24, 46, 53, 71, and 90. The number of protease mutations from the 11 identified in these analyses (the **lopinavir** mutation score) may be useful for the interpretation of HIV genotypic resistance testing with respect of **lopinavir**-ritonavir (Kaletra) regimens and may provide insight into the genetic barrier to resistance to **lopinavir**-ritonavir in both antiretroviral therapy-naive and protease inhibitor-experienced patients.
CC 10-4 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 1
IT Anti-AIDS agents
Genotypes
Human **immunodeficiency** virus
(identification of genotypic changes in human **immunodeficiency** virus protease that correlate with reduced susceptibility to protease inhibitor **lopinavir** among viral isolates from protease

inhibitor-experienced patients)
IT 37205-61-1, protease inhibitor 144114-21-6, HIV protease 192725-17-0, **Lopinavir**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of genotypic changes in human **immunodeficiency** virus protease that correlate with reduced susceptibility to protease inhibitor **lopinavir** among viral isolates from protease inhibitor-experienced patients)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 63 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:445983 HCAPLUS
DOCUMENT NUMBER: 136:303303
TITLE: Antiviral drugs: current state of the art
AUTHOR(S): De Clercq, E.
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Journal of Clinical Virology (**2001**), 22(1), 73-89
CODEN: JCVIFB; ISSN: 1386-6532
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The chemotherapy of virus infections has definitely come of age. There are now 15 antiviral agents that have been formally licensed for the treatment of human **immunodeficiency** virus infections (zidovudine, didanosine, zalcitabine, stavudine, Lamivudine, Abacavir, Nevirapine, Delavirdine, Efavirenz, Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, **Lopinavir**) and several others, such as Tenofovir Disoproxil, Emtricitabine, Capravirine, Emivirine, T-20 (Pentafuside), and AMD3100 (bicyclam), are under clin. development. Lamivudine has been approved, and several other compds. (such as Adefovir Dipivoxil, Emtricitabine, and Entecavir) are under clin. development, for the treatment of hepatitis B virus infections. Among the anti-herpesvirus agents, Aciclovir, Valaciclovir, Penciclovir, Famciclovir, Idoxuridine, Trifluridine, and Brivudin are used in the treatment of herpes simplex virus and varicella-zoster virus infections, and Ganciclovir, Foscarnet, Cidofovir, Fomivirsen, and Maribavir (the latter in the developmental stage) are used in the treatment of cytomegalovirus infections. Following amantadine and Rimantadine, the neuraminidase inhibitors, Zanamivir and Oseltamivir, have now become available for the therapy and prophylaxis of influenza virus infections, and so is Ribavirin for the treatment of respiratory syncytial virus infections and the combination of Ribavirin with interferon-α for the treatment of hepatitis C virus infections.
CC 1-0 (Pharmacology)

L19 ANSWER 64 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:402293 HCAPLUS
DOCUMENT NUMBER: 135:195771
TITLE: Synthesis and antiviral activities of the major metabolites of the HIV protease inhibitor ABT-378 (Lopinavir)
AUTHOR(S): Sham, H. L.; Betebenner, D. A.; Herrin, T.; Kumar, G.; Saldivar, A.; Vasavanonda, S.; Molla, A.; Kempf, D. J.; Plattner, J. J.; Norbeck, D. W.
CORPORATE SOURCE: Pharmaceutical Discovery, Abbott Laboratories, Abbott Park, IL, 60064-6101, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**2001**

), 11(11), 1351-1353
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:195771

AB The HIV protease inhibitor ABT-378 (Lopinavir) is metabolized rapidly and extensively by CYP-3A4 catalyzed oxidation Three of the major metabolites identified were synthesized and their antiviral (HIV) activities determined A concise synthesis of the major metabolites M-1 and M-3/M-4 of the protease inhibitor ABT-378 is described.

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

IT Antiviral agents
Human **immunodeficiency** virus
(synthesis and antiviral activities of metabolites of HIV protease inhibitor ABT-378 (**Lopinavir**))

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 65 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:382849 HCAPLUS
DOCUMENT NUMBER: 135:235745
TITLE: Effect of reduced-dose amprenavir in combination with lopinavir on plasma levels of amprenavir in patients infected with HIV
AUTHOR(S): Stein, Allan J.; Brothers, Cynthia H.; Scott, Trevor R.
CORPORATE SOURCE: Care Resource, Coral Gables, FL, USA
SOURCE: Clinical Therapeutics (**2001**), 23(3), 513-515
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 4 refs. Although protease inhibitors are an effective therapy for patients infected with HIV. the large number of daily pills required for these regimens often results in suboptimal adherence to treatment. Recent data have shown that. in patients who have not been treated previously with antiretroviral agents, virol. outcome is directly associated with a lower pill burden.'. Due to its potency as an inhibitor of the cytochrome P 450 isoenzyme 3A4 (CYP 3A4), ritonavir in low doses (eg, 100 or 200 mg BID) is increasingly being used to enhance the pharmacokinetic effects of HIV protease inhibitors. This strategy generally allows increased exposure to the protease inhibitor while decreasing the daily pill burden by up to 50%. Amprenavir is an HIV protease inhibitor indicated for the treatment of HIV infection. Both amprenavir and ritonavir are substrates and inhibitors of CYP 3A4. Clin. data have shown that the combination of amprenavir 600 mg BID plus ritonavir 100 mg BID delivers higher steady-state plasma trough concns. (Cmin.) of amprenavir (-5-fold increase) compared with the currently approved dosage of amprenavir (1200mg BID). Lopinavir is a new HIV protease inhibitor approved in the United States for the treatment of HIV infection. It is coformulated with ritonavir as a pharmacokinetic-enhancing agent. We evaluated 6 male patients (median age 45 yr: range 36-50 yr) at a single clinic who received reduced-dose amprenavir plus lopinavir (400mg lopinavir BID plus ritonavir 100 mg BID). We observed significant, albeit variable, pharmacokinetic enhancement of amprenavir steady-state trough values relative to those obtained with the approved amprenavir dose when amprenavir was coadministered with

lopinavir/ritonavir. These data suggest that an amprenavir dosage of 600 mg or 750 mg BID in combination with lopinavir/ritonavir-and in the absence of non-nucleoside reverse transcriptase inhibitors-is appropriate when coadministered to patients infected with HIV-I infection. Larger, long-term controlled trials are needed to confirm and investigate the possible significance of this anecdotal observation. The measurement of plasma levels of drug is likely to be useful in monitoring individual dosing needs as well as adherence to treatment.

CC 1-0 (Pharmacology)

IT Anti-AIDS agents
Human **immunodeficiency** virus 1
(effect of reduced-dose amprenavir in combination with **lopinavir** on plasma levels of amprenavir in humans infected with HIV)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 66 OF 93 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:41286 HCAPLUS
DOCUMENT NUMBER: 135:116204
TITLE: Lopinavir
AUTHOR(S): Hurst, Miriam; Faulds, Diana
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (**2000**), 60(6), 1371-1379
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 38 refs. Lopinavir is a protease inhibitor with high specificity for HIV-1 protease. Ritonavir strongly inhibits lopinavir metabolism; coadministration of lopinavir and ritonavir in healthy volunteers increased the area under the lopinavir plasma concentration-time curve >100-fold.
Trough plasma concentration: antiviral 50% effective concentration ratio for lopinavir
was >75 for wild-type HIV at the dose used in clin. trials, compared to values of ≤4 for other commonly used protease inhibitors. Coformulated lopinavir and ritonavir (lopinavir/ritonavir) 400/100mg twice daily for 48 wk suppressed HIV replication in significantly more anti-retroviral-naive patients than nelfinavir 750mg 3 times daily (all patients also received stavudine and lamivudine). Suppression of viral replication was observed in most protease inhibitor-experienced patients with lopinavir/ritonavir (400/100, 400/200 or 533/133mg twice daily for 48 or 96 wk) in combination with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs) and either efavirenz or nevirapine. 48 Wk of treatment with twice daily lopinavir/ritonavir (230/57.5 or 300/75 mg/m2 for the first 12 wk and then 300/75 mg/m2) in combination with 1 or 2 NRTIs, with or without nevirapine, suppressed viral replication in the majority of antiretroviral-naive and -experienced paediatric patients (aged 6 mo to 12 yr). Diarrhea, nausea and asthenia were the most frequently reported adverse effects in patients receiving lopinavir/ritonavir-based regimens. Elevated total cholesterol, triglyceride and hepatic enzyme levels were also reported.

CC 1-0 (Pharmacology)

IT Anti-AIDS agents
Human **immunodeficiency** virus 1
(**lopinavir**, antiretroviral drug, for treatment of HIV infections in humans)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS

L19 ANSWER 67 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2004035206 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14735233
TITLE: Gateways to clinical trials.
AUTHOR: Bayes M; Rabasseda X; Prous J R
CORPORATE SOURCE: Prous Science, Barcelona, Spain.. mbayes@prous.com
SOURCE: Methods and findings in experimental and clinical pharmacology, **(2003 Dec)** Vol. 25, No. 10, pp. 831-55.
Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040122
Last Updated on STN: 20040501
Entered Medline: 20040430

AB Gateways to Clinical Trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies Knowledge Area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: Abetimus sodium, adalimumab, alefacept, alemtuzumab, almotriptan, AMGN-0007, anakinra, anti-CTLA-4 Mab, L-arginine hydrochloride, arzoxifene hydrochloride, astemizole, atazanavir sulfate, atlizumab; Belimumab, BG-9928, binodenoson, bosentan, botulinum toxin type B, **bovine** lactoferrin, BufferGel; Caspofungin acetate, ciclesonide,cilomilast, ciluprevir, clofarabine, CVT-3146; Darbepoetin alfa, desloratadine, diflomotecan, doripenem, dronedarone hydrochloride, drotrecogin alfa (activated), DT388-GM-CSF, duloxetine hydrochloride, E-5564, efalizumab, enfuvirtide, esomeprazole magnesium, estradiol acetate, ETC-642, exenatide, exisulind, ezetimib; Febuxostat; Gallium maltolate, ganirelix acetate, garenoxacin mesilate, gefitinib; H11, HuMax; IL-15, IDD-1, IGIV-C, imatinib mesylate, ISIS-14803, ITF-1697, ivabradine hydrochloride; KRN-5500; L-365260, levetiracetam, levosimendan, licofelone, linezolid, LJP-1082, **lopinavir** lumiracoxib; MCC-478, melatonin, morphine hydrochloride, morphine-6-glucuronide, moxidectin; N-Acetylcarnosine, natalizumab, NM-702, NNC-05-1869, NSC-703940; Ocinaplon OM-89, omalizumab, omeprazole/ sodium bicarbonate, OPC-28326, ospemifene; PEG-filgrastim peginterferon alfa-2a, pegsunercept, pirfenidone, pralmorelin, pregabalin; Recombinant glucagon-like peptide-1 (7-36) amide, repifermin, RSD-1235; S-8184, selodenoson, sodium dichloroacetate, suberanilohydroxamic acid; TAS-102, terfenadine, teriparatide, tipranavir troxacitabine; Ximelagatran; YM-337.

CT *Clinical Trials
*Drug Therapy
Humans

L19 ANSWER 68 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003605098 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14689363
TITLE: Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired **immunodeficiency** syndrome: the role of **lopinavir**-ritonavir-didanosine.

AUTHOR: Rollot Florence; Nazal Eve-Marie; Chauvelot-Moachon Laurence; Kelaidi Charikleia; Daniel Nathalie; Saba Mona; Abad Sebastien; Blanche Philippe
CORPORATE SOURCE: Internal Medicine, Cochin and Saint Vincent de Paul Hospital, Paris, France.
SOURCE: Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, **(2003 Dec 15)** Vol. 37, No. 12, pp. e174-6. Electronic Publication: 2003-11-18.
Journal code: 9203213. E-ISSN: 1537-6591.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20031223
Last Updated on STN: 20040218
Entered Medline: 20040217

AB Tenofovir-related tubular damage, like all other recently reported cases, occurred in patients receiving the protease inhibitor (PI) ritonavir, often with lopinavir. Increased plasma concentrations of didanosine were also observed after the addition of tenofovir. It was suspected that tenofovir with PIs interacted with renal organic anion transporters, leading to nephrotoxic tubular concentrations of tenofovir and systemic accumulation of didanosine. Until there is a better understanding of these interactions, close monitoring is recommended for patients receiving tenofovir, PIs, and didanosine.

CT Check Tags: Male
Acquired Immunodeficiency Syndrome: CO, complications
*Acquired Immunodeficiency Syndrome: DT, drug therapy
*Adenine: AA, analogs & derivatives
Adult
*Anti-HIV Agents: TU, therapeutic use
*Diabetes Insipidus, Nephrogenic: CO, complications
Didanosine: TU, therapeutic use
Drug Therapy, Combination
Fanconi Syndrome: CI, chemically induced
*Fanconi Syndrome: CO, complications
Humans
Organophosphorus Compounds
*Phosphonic Acids
Pyrimidinones: TU, therapeutic use
Ritonavir: TU, therapeutic use

RN 107021-12-5 (tenofovir); 192725-17-0 (lopinavir); 69655-05-6 (Didanosine); 73-24-5 (Adenine)
CN 0 (Anti-HIV Agents); 0 (Organophosphorus Compounds); 0 (Phosphonic Acids); 0 (Pyrimidinones); 0 (Ritonavir)

L19 ANSWER 69 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003553392 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14632538
TITLE: Tacrolimus and lopinavir/ritonavir interaction in liver transplantation.
AUTHOR: Schonder Kristine S; Shullo Michael A; Okusanya Olanrewaju
CORPORATE SOURCE: University of Pittsburgh School of Pharmacy and University of Pittsburgh Medical Center, Pittsburgh, PA, USA.. schonderks@msx.upmc.edu
SOURCE: The Annals of pharmacotherapy, **(2003 Dec)** Vol.

37, No. 12, pp. 1793-6.
Journal code: 9203131. ISSN: 1060-0280.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20031125
Last Updated on STN: 20040414
Entered Medline: 20040413

AB OBJECTIVE: To report an interaction between tacrolimus and the protease inhibitor combination **lopinavir**/ritonavir in a liver transplant patient.CASE SUMMARY: A 48-year-old white male liver transplant recipient receiving tacrolimus 5 mg twice daily for **immunosuppression** started highly active antiretroviral therapy for his HIV-positive status. Three days after initiation of **lopinavir**/ritonavir, the tacrolimus concentration rose sharply to toxic levels. Subsequent tacrolimus doses were withheld until tacrolimus concentrations normalized over 15 days. The tacrolimus dose was reestablished at a much lower dose, 0.5 mg once weekly. An objective causality assessment revealed that the adverse event was highly probable.DISCUSSION: Tacrolimus is metabolized in the liver via CYP3A4. Protease inhibitors are known to inhibit CYP3A4 and have been documented to increase tacrolimus concentrations, putting the patient at risk of developing nephrotoxic and/or neurotoxic symptoms. In this case, concomitant use of **lopinavir**/ritonavir caused tacrolimus concentrations to rise more dramatically than had been previously reported in the literature for other protease inhibitors.CONCLUSIONS: Extreme caution must be used when administering tacrolimus concomitantly with **lopinavir**/ritonavir. Therapeutic concentrations of tacrolimus can be maintained with tacrolimus doses that are far below standard dosages.

CT Check Tags: Male
Drug Interactions: PH, physiology
Graft Rejection: BL, blood
Graft Rejection: DT, drug therapy
Humans
*Liver Transplantation
Liver Transplantation: MT, methods
Middle Aged
*Pyrimidinones: BL, blood
Pyrimidinones: TU, therapeutic use
*Ritonavir: BL, blood
Ritonavir: TU, therapeutic use
*Tacrolimus: BL, blood
Tacrolimus: TU, therapeutic use

RN 109581-93-3 (Tacrolimus); 192725-17-0 (lopinavir)
CN 0 (Pyrimidinones); 0 (Ritonavir)

L19 ANSWER 70 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003419181 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12942457
TITLE: Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients.
AUTHOR: Jain Ashokkumar B; Venkataramanan Raman; Eghtesad Bijan; Marcos Amadeo; Ragni Margaret; Shapiro Ron; Rafail Ann B; Fung John J
CORPORATE SOURCE: Department of Surgery, Division of Transplantation, Thomas

E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, USA..
ashok_jain@urmc.rochester.edu
SOURCE: Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society, **(2003 Sep)** Vol. 9, No. 9, pp. 954-60.
Journal code: 100909185. ISSN: 1527-6465.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030909
Last Updated on STN: 20040106
Entered Medline: 20040105

AB With the advent of highly active antiretroviral therapy (HAART), HIV positivity is no longer a contraindication for liver transplantation. Some of the antiretroviral agents, particularly protease inhibitors (e.g., ritonavir, indinavir, and nelfinavir) have been described as potent inhibitors of the metabolism of certain **immunosuppressive** drugs. In this article we describe a profound interaction between tacrolimus and Kaletra (Abbott Laboratories, Chicago, IL) (a combination of **lopinavir** and ritonavir) in 3 liver transplantation patients. Patient 1, who was maintained on a 5 mg twice daily dose of tacrolimus with a trough blood concentration around 10.6 ng/mL, required only 0.5 mg of tacrolimus per week after addition of Kaletra to achieve similar tacrolimus blood concentrations, with a half-life of 10.6 days. In patient 2, the area under the blood concentration versus time curve for tacrolimus increased from 31 ng/mL/h to 301 ng/mL/h after addition of Kaletra, with a corresponding half-life of 20 days. When the patient was subsequently switched to nelfinavir, the half-life decreased to 10.3 days. Patient 3, who was maintained with 4 to 8 mg/d of tacrolimus and a corresponding blood concentration of 10 ng/mL before Kaletra, required a tacrolimus dose of 1 mg/wk and tacrolimus concentrations of 5 ng/mL with Kaletra. In conclusion, a combination of **lopinavir** and ritonavir led to a much more profound increase in tacrolimus blood concentrations than use of single protease inhibitor, nelfinavir. A tacrolimus dose of less than 1 mg/wk may be sufficient to maintain adequate blood tacrolimus concentrations in patients on Kaletra. Patients may not need a further dose of tacrolimus for 3 to 5 weeks depending on liver function when therapy with Kaletra is initiated. Great caution is required in the management of tacrolimus dosage when Kaletra is introduced or withdrawn in HIV-positive patients after liver transplantation, particularly in the presence of hepatic dysfunction.

CT Check Tags: Female; Male
Adult
Drug Interactions
Drug Therapy, Combination
*HIV Infections: DT, drug therapy
*HIV Protease Inhibitors: AD, administration & dosage
Humans
Immunosuppressive Agents: BL, blood
*Immunosuppressive Agents: PK, pharmacokinetics
*Liver Diseases: CO, complications
Liver Diseases: SU, surgery
*Liver Transplantation
Middle Aged

*Pyrimidinones: AD, administration & dosage
*Ritonavir: AD, administration & dosage
Tacrolimus: BL, blood
*Tacrolimus: PK, pharmacokinetics
RN 109581-93-3 (Tacrolimus); 192725-17-0 (lopinavir)
CN 0 (HIV Protease Inhibitors); 0 (Immunosuppressive Agents); 0 (Pyrimidinones); 0 (Ritonavir)

L19 ANSWER 71 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003396108 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12934180
TITLE: Enhanced prediction of lopinavir resistance from genotype by use of artificial neural networks.
AUTHOR: Wang Dechao; Larder Brendan
CORPORATE SOURCE: Virco, Cambridge, United Kingdom.. dechaowang@hivrdi.org
SOURCE: The Journal of infectious diseases, **(2003 Sep 1)** Vol. 188, No. 5, pp. 653-60. Electronic Publication: 2003-08-14.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030823
Last Updated on STN: 20031010
Entered Medline: 20031009

AB Our objective was to accurately predict, from complex mutation patterns, human **immunodeficiency** virus type 1 resistance to the protease inhibitor **lopinavir**, by use of artificial intelligence. Two neural network models were constructed: 1 based on changes at 11 positions in the protease that were previously recognized as being significant for **lopinavir** resistance and another based on a newly derived set of 28 mutations that were identified by performing category prevalence analysis. Both models were trained, validated, and tested with 1322 clinical samples. A procedure of determining the optimal neural network parameters was proposed to speed up the training processes. The results suggested that the 28-mutation set was a more accurate predictor of **lopinavir** susceptibility (correlation coefficient, R2=0.88). We identified potentially significant new mutations associated with **lopinavir** resistance and demonstrated the utility of neural network models in predicting phenotypic susceptibility from complex genotypes.

CT *Drug Resistance, Viral: GE, genetics
Genotype
HIV Infections: VI, virology
HIV Protease: GE, genetics
*HIV Protease Inhibitors: PD, pharmacology
*HIV-1: DE, drug effects
HIV-1: EN, enzymology
HIV-1: GE, genetics
Humans
Microbial Sensitivity Tests: MT, methods
Mutation
*Neural Networks (Computer)
Phenotype
Predictive Value of Tests
*Pyrimidinones: PD, pharmacology
RN 192725-17-0 (lopinavir)

CN 0 (HIV Protease Inhibitors); 0 (Pyrimidinones); EC 3.4.23.- (HIV Protease)

L19 ANSWER 72 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003221977 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12743628
TITLE: Gateways to clinical trials.
AUTHOR: Bayes M; Rabasseda X; Prous J R
CORPORATE SOURCE: Medical Information Department, Prous Science, Barcelona, Spain.. mbayes@prous.com
SOURCE: Methods and findings in experimental and clinical pharmacology, **(2003 Apr)** Vol. 25, No. 3, pp. 225-48. Ref: 152
Journal code: 7909595. ISSN: 0379-0355.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030514
Last Updated on STN: 20030910
Entered Medline: 20030909

AB Gateways to clinical trials is a guide to the most recent clinical trials in current literature and congresses. The data in the following tables has been retrieved from the Clinical Studies knowledge area of Prous Science Integrity, the drug discovery and development portal, http://integrity.prous.com. This issue focuses on the following selection of drugs: 5A8; Agomelatine, alefacept, almotriptan, anakinra, APC-8015, atazanavir, atomoxetine hydrochloride, azimilide hydrochloride; Bicifadine; Cannabidiol, caspofungin acetate, CAT-213, CGP-51901, ciclesonide, cipamfylline; Darbepoetin alfa, desloratadine, dibotermin alfa, DX-9065a; Ecogramostim, efalizumab, eletriptan, eniluracil, EPI-KAL2, erlosamide, ertapenem sodium, etilevodopa, etoricoxib, ezetimibe; Fosamprenavir calcium, fosamprenavir sodium, fumagillin; Gadofosveset sodium, gefitinib, gemtuzumab ozogamicin; HSPPC-96, human papillomavirus vaccine; Icatibant Id-**KLH**, imatinib mesylate, INS-37217, iodine (I131) tositumomab; LAS-34475, levobupivacaine hydrochloride, levocetirizine, linezolid, 131I-lipiodol, lonafarnib, **lopinavir**, LY-450108; Magnetites, MBI-594AN, melagatran, melatonin, mepolizumab, mycophenolic acid sodium salt; NC-100100; 1-Octanol, omalizumab, omapatrilat, onercept; PEG-filgrastim, (PE)HRG21, peginterferon alfa-2a, peginterferon alfa-2b, pleconaril, pneumococcal 7-valent conjugate vaccine, prasterone; Ranelic acid distrontium salt, rasagiline mesilate, reslizumab, rFGF-2, rhOP-1, rosuvastatin calcium, roxifiban acetate; Sitaxsentan sodium, sodium lauryl sulfate; Tadalafil, telithromycin, tenofovir disoproxil fumarate, tipranavir, TMC-114, tucaresol; Valdecoxib, voriconazole; Ximelagatran; Zofenopril calcium, zosuquidar trihydrochloride.

CT Double-Blind Method
*Drug Therapy
Humans
*Randomized Controlled Trials

L19 ANSWER 73 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003180878 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12700464
TITLE: Lopinavir: acute exposure inhibits P-glycoprotein; extended exposure induces P-glycoprotein.

AUTHOR: Vishnuvardhan Daesety; Moltke Lisa L; Richert Clemens; Greenblatt David J
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111, USA.
CONTRACT NUMBER: AG-17880 (NIA)
DA-05258 (NIDA)
DA-13209 (NIDA)
DA-13834 (NIDA)
DK/AI-58496 (NIDDK)
MH-01237 (NIMH)
MH-58435 (NIMH)
RR-00054 (NCRR)
SOURCE: AIDS (London, England), **(2003 May 2)** Vol. 17, No. 7, pp. 1092-4.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030418
Last Updated on STN: 20030624
Entered Medline: 20030623

AB The effect of **lopinavir** on P-glycoprotein-mediated rhodamine 123 efflux was studied in Caco-2 monolayer cells. **Lopinavir** is a potent inhibitor of Rh123 efflux in Caco-2 monolayers (IC50 1.7 microM). Chronic **lopinavir** exposure (72 h) in LS 180V cells reduced the content of intracellular Rh123 by approximately 50%, indicating increased efflux activity. In LS 180V cells, **lopinavir** induced P-glycoprotein **immunoreactive** protein (up to threefold) and messenger RNA levels in a concentration-dependent fashion.

CT *Anti-HIV Agents: PD, pharmacology
Blotting, Western
Caco-2 Cells
Dose-Response Relationship, Drug
Fluorescent Dyes: ME, metabolism
*HIV Protease Inhibitors: PD, pharmacology
Humans
*P-Glycoprotein: AI, antagonists & inhibitors
*Pyrimidinones: PD, pharmacology
RNA, Messenger: ME, metabolism
RNA, Viral: ME, metabolism
Research Support, U.S. Gov't, P.H.S.
Rhodamine 123: AI, antagonists & inhibitors
Time Factors

RN 192725-17-0 (lopinavir); 62669-70-9 (Rhodamine 123)
CN 0 (Anti-HIV Agents); 0 (Fluorescent Dyes); 0 (HIV Protease Inhibitors); 0 (P-Glycoprotein); 0 (Pyrimidinones); 0 (RNA, Messenger); 0 (RNA, Viral)

L19 ANSWER 74 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003143336 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12634581
TITLE: Forty-eight-week evaluation of **lopinavir** /ritonavir, a new protease inhibitor, in human **immunodeficiency** virus-infected children.
AUTHOR: Saez-Llorens Xavier; Violari Avyi; Deetz Carl O; Rode Richard A; Gomez Perry; Handelsman Edward; Pelton Stephen; Ramilo Octavio; Cahn Pedro; Chadwick Ellen; Allen Upton; Arpadi Stephen; Castrejon Maria Mercedes; Heuser Renee S;

Kempf Dale J; Bertz Richard J; Hsu Ann F; Bernstein Barry; Renz Cheryl L; Sun Eugene
CORPORATE SOURCE: Hospital del Nino, Panama City, Panama..
xsaezll@cwpanama.net
SOURCE: The Pediatric infectious disease journal, **(2003 Mar)** Vol. 22, No. 3, pp. 216-24.
Journal code: 8701858. ISSN: 0891-3668.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030328
Last Updated on STN: 20030529
Entered Medline: 20030528

AB BACKGROUND: **Lopinavir**/ritonavir has demonstrated antiviral activity in the HIV-infected adult. SUBJECTS: The objective of this study was to investigate a liquid coformulation of **lopinavir** /ritonavir, in combination with reverse transcriptase inhibitors, in HIV-infected children. METHODS: One hundred antiretroviral (ARV)-naive and ARV-experienced, nonnucleoside reverse transcriptase inhibitor-naive children between 6 months and 12 years of age participated in this Phase I/II, open **label**, multicenter trial. Subjects initially received either 230/57.5 mg/m(2) or 300/75 mg/m(2) **lopinavir** /ritonavir twice daily; ARV-naive subjects also received stavudine and lamivudine, whereas ARV-experienced subjects also received nevirapine and one or two nucleoside reverse transcriptase inhibitors. **Lopinavir** /ritonavir pharmacokinetics, safety and efficacy were evaluated. RESULTS: All subjects were escalated to the 300/75 mg/m(2) twice daily dose based on results from an interim pharmacokinetic and safety evaluation. The pharmacokinetics of **lopinavir** did not appear to be dependent on age when dosing was based on body surface area but were decreased on coadministration with nevirapine. Overall 79% of subjects had HIV RNA levels <400 copies/ml at Week 48 (intent-to-treat: missing = failure). Mean increases in absolute and relative (percent) CD4 counts from baseline to Week 48 were observed in both ARV-naive subjects (404 cells/mm(3); 10.3%) and ARV-experienced subjects (284 cells/mm(3); 5.9%). Only one subject prematurely discontinued the study because of a study drug-related adverse event. CONCLUSIONS: The liquid coformulation of **lopinavir** /ritonavir demonstrated durable antiviral activity and was safe and well-tolerated after 48 weeks of treatment in HIV-infected children.

CT Check Tags: Female; Male
Administration, Oral
Biological Availability
Chemistry, Pharmaceutical
Child
Child, Preschool
Comparative Study
Confidence Intervals
Dose-Response Relationship, Drug
Drug Administration Schedule
Drug Therapy, Combination
Follow-Up Studies
HIV Infections: DI, diagnosis
*HIV Infections: DT, drug therapy

Humans
Infant
*Maximum Tolerated Dose
Multivariate Analysis
*Pyrimidinones: AD, administration & dosage
Pyrimidinones: PK, pharmacokinetics
RNA, Viral: DE, drug effects
Research Support, Non-U.S. Gov't
*Reverse Transcriptase Inhibitors: AD, administration & dosage
Reverse Transcriptase Inhibitors: PK, pharmacokinetics
*Ritonavir: AD, administration & dosage
Ritonavir: PK, pharmacokinetics
Severity of Illness Index
Time Factors
Treatment Outcome
Viral Load
RN 192725-17-0 (lopinavir)
CN 0 (Pyrimidinones); 0 (RNA, Viral); 0 (Reverse Transcriptase Inhibitors); 0 (Ritonavir)

L19 ANSWER 75 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2003091903 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12604531
TITLE: High variability of plasma drug concentrations in dual protease inhibitor regimens.
AUTHOR: Guiard-Schmid Jean-Baptiste; Poirier Jean-Marie; Meynard Jean-Luc; Bonnard Philippe; Gbadoe Ayi Hola; Amiel Corinne; Calligaris Frederique; Abraham Bruno; Pialoux Gilles; Girard Pierre-Marie; Jaillon Patrice; Rozenbaum Willy
CORPORATE SOURCE: Department of Clinical Infectious and Tropical Diseases, Tenon Hospital, Paris, France.. jean-baptiste.guiard-schmid@tnn.ap-hop-paris.fr
SOURCE: Antimicrobial agents and chemotherapy, **(2003 Mar)** Vol. 47, No. 3, pp. 986-90.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030227
Last Updated on STN: 20030815
Entered Medline: 20030814

AB Ritonavir (RTV) strongly increases the concentrations of protease inhibitors (PIs) in plasma in patients given a combination of RTV and another PI. This pharmacological interaction is complex and poorly characterized and shows marked inter- and intraindividual variations. In addition, RTV interacts differently with saquinavir (SQV), indinavir (IDV), amprenavir (APV), and **lopinavir** (LPV). In this retrospective study on 542 human **immunodeficiency** virus-infected patients, we compared inter- and intraindividual variability of plasma PI concentrations and correlations between the C(min) (minimum concentration of drug in plasma) values for RTV and the coadministered PI C(min) values. Mean RTV C(min)s are significantly lower in patients receiving combinations containing APV or LPV than in combinations with SQV or IDV. With the most common PI dose regimens (600 mg of IDV twice a day [BID], 800 mg of SQV BID, and 400 mg of LPV BID), the interindividual C(min) variability of patients treated with a PI and RTV seemed to be lower with APV and LPV than with IDV and SQV. As regards intraindividual

variability, APV also differed from the other PIs, exhibiting lower C(min) variability than with the other combinations. Significant positive correlations between RTV C(min) and boosted PI C(min) were observed with IDV, SQV, and LPV, but not with APV. Individual dose adjustments must take into account the specificity the pharmacological interaction of each RTV/PI combination and the large inter- and intraindividual variability of plasma PI levels to avoid suboptimal plasma drug concentrations which may lead to treatment failure and too high concentrations which may induce toxicity and therefore reduce patient compliance.

CT Anti-HIV Agents: AD, administration & dosage
*Anti-HIV Agents: BL, blood
Anti-HIV Agents: TU, therapeutic use
Drug Interactions
Drug Therapy, Combination
Humans
Retrospective Studies
Reverse Transcriptase Inhibitors: AD, administration & dosage
*Reverse Transcriptase Inhibitors: BL, blood
Reverse Transcriptase Inhibitors: TU, therapeutic use
Ritonavir: AD, administration & dosage
*Ritonavir: BL, blood
Ritonavir: TU, therapeutic use
CN 0 (Anti-HIV Agents); 0 (Reverse Transcriptase Inhibitors); 0 (Ritonavir)

L19 ANSWER 76 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002625852 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12384393
TITLE: **Lopinavir** measurement in pleural effusion in a human **immunodeficiency** virus type 1-infected patient with kaposi's sarcoma.
AUTHOR: Boffito Marta; Hoggard Patrick G; Back David J; Bonora Stefano; Maiello Agostino; Lucchini Anna; Di Perri Giovanni
SOURCE: Antimicrobial agents and chemotherapy, **(2002 Nov)** Vol. 46, No. 11, pp. 3684-5.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021018
Last Updated on STN: 20030325
Entered Medline: 20030324
CT *HIV Infections: ME, metabolism
*HIV Protease Inhibitors: AN, analysis
HIV Protease Inhibitors: PK, pharmacokinetics
*HIV-1
Humans
*Pleural Effusion: CH, chemistry
*Pyrimidinones: AN, analysis
Pyrimidinones: PK, pharmacokinetics
*Sarcoma, Kaposi: ME, metabolism
RN 192725-17-0 (lopinavir)
CN 0 (HIV Protease Inhibitors); 0 (Pyrimidinones)

L19 ANSWER 77 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002613186 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12370509
TITLE: Clinical use of lopinavir/ritonavir in a salvage therapy

setting: pharmacokinetics and pharmacodynamics.
AUTHOR: Boffito Marta; Arnaudo Isabella; Raiteri Riccardo; Bonora Stefano; Sinicco Alessandro; Di Garbo Antonio; Reynolds Helen E; Hoggard Patrick G; Back David J; Di Perri Giovanni
CORPORATE SOURCE: Department of Infectious Diseases, University of Torino, Turin, Italy.
SOURCE: AIDS (London, England), **(2002 Oct 18)** Vol. 16, No. 15, pp. 2081-3.
Journal code: 8710219. ISSN: 0269-9370.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20021010
Last Updated on STN: 20021214
Entered Medline: 20021126

AB **Lopinavir**/ritonavir was administered to 35 HIV-infected patients after therapeutic failure with other protease inhibitors. The pharmacokinetics (trough concentrations) and baseline viral genotype were determined, together with the **immunovirological** outcome. The 22 responders had significantly higher mean **lopinavir** concentrations and lower baseline numbers of mutations. On multivariate analysis, a **lopinavir** concentration of 5.7 microg/ml or greater was an independent predictor of viral suppression over a 9-month follow-up period.

CT Check Tags: Female; Male
CD4 Lymphocyte Count
*HIV Infections: DT, drug therapy
HIV Infections: IM, immunology
HIV Infections: VI, virology
HIV Protease: GE, genetics
*HIV Protease Inhibitors: PK, pharmacokinetics
HIV Protease Inhibitors: TU, therapeutic use
HIV-1: PH, physiology
Humans
Mutation
*Pyrimidinones: PK, pharmacokinetics
Pyrimidinones: TU, therapeutic use
Research Support, Non-U.S. Gov't
*Ritonavir: PK, pharmacokinetics
Ritonavir: TU, therapeutic use
*Salvage Therapy
Treatment Outcome
Viral Load

RN 192725-17-0 (lopinavir)
CN 0 (HIV Protease Inhibitors); 0 (Pyrimidinones); 0 (Ritonavir); EC 3.4.23.- (HIV Protease)

L19 ANSWER 78 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002500311 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 12361546
TITLE: [Approach to treatment of patients with virologic failure to multiple regimens].
Aproximacion al tratamiento del paciente en situacion de multifracaso.
AUTHOR: Riera Melcior; Ribas Maria Angels; Perez Elias Maria Jesus; Mallolas Josep; Portilla Joaquim; Viciana Pompeyo
CORPORATE SOURCE: Hospitales Son Dureta (Palma de Mallorca).

SOURCE: Enfermedades infecciosas y microbiologia clinica, **(2002 Jul)** Vol. 20 Suppl 2, pp. 58-67.
Journal code: 9104081. ISSN: 0213-005X.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Spanish
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021004
Last Updated on STN: 20021213

AB Second-line and rescue antiretrovirals regimens have a poor success record only 30-45% achieves viral suppression. This rate will be improved if salvage therapy is individualized with a better understanding what causes previous failures, establishing reasonable goals of therapy for the patient and speaking with him about the pros and the cons of the new regimens.Before deciding the change we must have available the first and the present HIV RNA levels, absolute CD4 T cell count and changes in these counts, prior antiretroviral therapies, resistance test, assessment of adherence to medications, and preparation of the patient for the implications of the new regimens. Carrying out drug salvage levels and the inhibitory quotient probably can be important.In patients on therapy with detectable but low (< 5,000 copies/ml) stable HIV RNA levels the risk of clinical or **immunologic** failure is low. Recent reports provide support for a conservative strategy, particularly for those patients with limited therapeutic options.In-patients who are failing their second regimen it is important to use at least two new susceptible drugs, with a high potency and using combinations that assure high drug levels. In this population treatment interruption as a strategy for managing drug resistance is in study.New therapies such as DAPD, tenofovir, TMC 120, **lopinavir**, tipranavir and T-20 offer significant promise for the treatment of drug-experienced patients.

L19 ANSWER 79 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002395957 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12145735
TITLE: Serious bradyarrhythmia that was possibly induced by **lopinavir**-ritonavir in 2 patients with acquired **immunodeficiency** syndrome.
AUTHOR: Kikuchi Yoshimi; Genka Ikumi; Ishizaki Azumi; Sunagawa Keishin; Yasuoka Akira; Oka Shinichi
CORPORATE SOURCE: AIDS Clinical Center, International Medical Center of Japan, Tokyo.
SOURCE: Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, **(2002 Aug 15)** Vol. 35, No. 4, pp. 488-90. Electronic Publication: 2002-07-17.
Journal code: 9203213. E-ISSN: 1537-6591.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020730
Last Updated on STN: 20030105
Entered Medline: 20020808

AB We describe 2 patients with acquired **immunodeficiency** syndrome who had potentially fatal bradyarrhythmia that occurred shortly after commencement of antiretroviral therapy. **Lopinavir**-ritonavir was

the only drug that both patients were using.
CT Check Tags: Male
*Acquired Immunodeficiency Syndrome: CO, complications
Acquired Immunodeficiency Syndrome: DT, drug therapy
Adult
*Anti-HIV Agents: AE, adverse effects
Anti-HIV Agents: TU, therapeutic use
*Bradycardia: CI, chemically induced
Humans
Middle Aged
*Pyrimidinones: AE, adverse effects
Pyrimidinones: TU, therapeutic use
Research Support, Non-U.S. Gov't
*Ritonavir: AE, adverse effects
Ritonavir: TU, therapeutic use
RN 192725-17-0 (lopinavir)
CN 0 (Anti-HIV Agents); 0 (Pyrimidinones); 0 (Ritonavir)

L19 ANSWER 80 OF 93 MEDLINE on STN
ACCESSION NUMBER: 2002073440 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11802104
TITLE: Therapeutic drug monitoring of HIV protease inhibitors using high-performance liquid chromatography with ultraviolet or photodiode array detection.
AUTHOR: Leibenguth P; Le Guellec C; Besnier J M; Bastides F; Mace M; Gaudet M L; Autret-Leca E; Paintaud G
CORPORATE SOURCE: Department of Pharmacology, Tours University Hospital, Tours, France.
SOURCE: Therapeutic drug monitoring, **(2001 Dec)** Vol. 23, No. 6, pp. 679-88.
Journal code: 7909660. ISSN: 0163-4356.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020308
Entered Medline: 20020307
AB Published data suggest that therapeutic drug monitoring of human **immunodeficiency** virus protease inhibitors would improve the management of antiretroviral therapy. The authors have developed a high-pressure liquid chromatographic assay allowing simultaneous determination of six protease inhibitors (ritonavir, saquinavir, indinavir, nelfinavir, amprenavir, and **lopinavir**), using carbamazepine as internal standard. Detection was based on a dual wavelength ultraviolet spectrophotometer and can be improved by the use of a photodiode array detector. Monitoring was performed 1 month after initiation of therapy or in instances of therapeutic failure, side effects, suspicion of noncompliance, drug interactions, or malabsorption. Trough concentrations were 0.15 to 13.6 mg/L for ritonavir, 0.06 to 9.7 mg/L for indinavir, 0.03 to 5.5 mg/L for saquinavir, and 0.15 to 4.15 mg/L for nelfinavir. Concentrations below the limit of quantification were observed in 63/438 (14%) of the patients. Target concentrations are not well established, and reported in vitro inhibitory concentrations may be of limited value. The authors therefore chose to compare observed concentrations with mean plasma concentrations reported in clinical trials. Observed saquinavir and indinavir concentrations were often below or close to these target concentrations, particularly when used as a

single protease inhibitor. Concentration-controlled studies should now be used to select proper target concentrations for each protease inhibitor, either prescribed alone or in combination.

CT Area Under Curve
Chromatography, High Pressure Liquid
Cytochrome P-450 Enzyme System: PH, physiology
*Drug Monitoring
*HIV Protease Inhibitors: BL, blood
Humans
Mixed Function Oxygenases: PH, physiology
Sensitivity and Specificity

RN 9035-51-2 (Cytochrome P-450 Enzyme System)

CN 0 (HIV Protease Inhibitors); EC 1.- (Mixed Function Oxygenases); EC 1.14.14.1 (CYP3A protein, human)

L19 ANSWER 81 OF 93 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004183762 EMBASE
TITLE: [Antiretroviral Treatment of Adult Patients in the 2004]. ANTIRETROVIRUSNO LIJECENJE ODRASLIH BOLESNIKA U 2004. GODINI.
AUTHOR: Begovac J.
CORPORATE SOURCE: J. Begovac, Klin. Infekt. Bolesti Dr. F. M., Mirogojska cesta 8, 10000 Zagreb, Croatia
SOURCE: Medicus, (2003) Vol. 12, No. 2, pp. 237-242. .
Refs: 33
ISSN: 1330-013X CODEN: MEDCEH
COUNTRY: Croatia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Croatian
SUMMARY LANGUAGE: English; Croatian
ENTRY DATE: Entered STN: 28 May 2004
Last Updated on STN: 28 May 2004

AB New information and new drugs for the treatment of human **immunodeficiency** virus type 1 infection have expanded our options but also dilemmas on the choice of drugs, onset and change of treatment. For the year 2004 we recommend starting treatment for: 1) patients with symptomatic HIV disease, 2) asymptomatic patients with less than 200 CD4+ cell counts per mm(3) of blood, and 3) asymptomatic patients with CD4+ cell counts between 200 and 350 per mm(3) of blood, and a HIV1 RNA viral load greater than 60000 copies per ml of plasma or a rapidly declining CD4+ cell count (more than 80 cells per mm(3) in one year). We do not recommend treatment for asymptomatic patients with more than 350 CD4+ cells per mm(3). The initial treatment should include a non-nucleoside analogue or a boosted protease inhibitor supported by low doses of ritonavir, with two nucleoside analogues. On the basis of randomized controlled clinical trials performed so far, the initial treatment of efavirenz of **lopinavir**/ritonavir can be recommended. The comb[nation combination of three nucleoside analogues is not recommended for initial treatment. Treatment success is defined by achieving a non-measurable viremia (less than 50 copies of HIV1 RNA per ml plasma). In the case of successful treatment, the antiretroviral regimen can be modified by simpler and less toxic combinations due to either the patient's wish or adverse events. In the case of initial therapy failure, special attention should be paid to issues like compliance, HIV virus resistance and drug pharmacokinetics. If the drug fails, it is necessary

to test HIV virus resistance to drugs and adequate medication should be administered on the basis of this analysis.

CT Medical Descriptors:
*Human immunodeficiency virus infection: DT, drug therapy
*Human immunodeficiency virus infection: ET, etiology
Human immunodeficiency virus 1
cell count
virus load
low drug dose
side effect: SI, side effect
human
clinical trial
article
Drug Descriptors:
*RNA directed DNA polymerase inhibitor: CB, drug combination
*RNA directed DNA polymerase inhibitor: DO, drug dose
*RNA directed DNA polymerase inhibitor: DT, drug therapy
*proteinase inhibitor: CB, drug combination
*proteinase inhibitor: DO, drug dose
*proteinase inhibitor: DT, drug therapy
*nucleoside analog: DT, drug therapy
antiretrovirus agent: AE, adverse drug reaction
antiretrovirus agent: CB, drug combination
antiretrovirus agent: DO, drug dose
antiretrovirus agent: DT, drug therapy
zidovudine: CB, drug combination
zidovudine: DO, drug dose
zidovudine: DT, drug therapy
didanosine: CB, drug combination
didanosine: DO, drug dose
didanosine: DT, drug therapy
zalcitabine: DT, drug therapy
lamivudine: CB, drug combination
lamivudine: DT, drug therapy
stavudine: CB, drug combination
stavudine: DO, drug dose
stavudine: DT, drug therapy
abacavir: DT, drug therapy
lamivudine plus zidovudine: DT, drug therapy
abacavir plus lamivudine plus zidovudine: DT, drug therapy
emtricitabine: DT, drug therapy
tenofovir: DT, drug therapy
nevirapine: CB, drug combination
nevirapine: DT, drug therapy
delavirdine: DT, drug therapy
efavirenz: CB, drug combination
efavirenz: DT, drug therapy
indinavir: CB, drug combination
indinavir: DT, drug therapy
ritonavir: DT, drug therapy
nelfinavir: DT, drug therapy
saquinavir: CB, drug combination
saquinavir: DO, drug dose
saquinavir: DT, drug therapy
amprenavir: DO, drug dose
amprenavir: DT, drug therapy
amprenavir phosphate: DO, drug dose
amprenavir phosphate: DT, drug therapy
lopinavir plus ritonavir: DT, drug therapy

enfuvirtide: DT, drug therapy
RN (proteinase inhibitor) 37205-61-1; (zidovudine) 30516-87-1; (didanosine) 69655-05-6; (zalcitabine) 7481-89-2; (lamivudine) 134678-17-4, 134680-32-3; (stavudine) 3056-17-5; (abacavir) 136470-78-5, 188062-50-2; (emtricitabine) 137530-41-7, 143491-54-7, 143491-57-0; (tenofovir) 147127-19-3, 147127-20-6; (nevirapine) 129618-40-2; (delavirdine) 136817-59-9; (efavirenz) 154598-52-4; (indinavir) 150378-17-9, 157810-81-6, 180683-37-8; (ritonavir) 155213-67-5; (nelfinavir) 159989-64-7, 159989-65-8; (saquinavir) 127779-20-8, 149845-06-7; (amprenavir) 161814-49-9; (amprenavir phosphate) 226700-79-4, 226700-80-7, 226700-81-8; (enfuvirtide) 159519-65-0

L19 ANSWER 82 OF 93 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003410595 EMBASE
TITLE: Anti-retroviral therapy: An update.
AUTHOR: Vasudev K.; Vasudev A.; Kohli K.
CORPORATE SOURCE: Prof. K. Kohli, Department of Pharmacology, Lady Harringe Medical College, New Delhi-110001, India. kkohli15@yahoo.com
SOURCE: Journal International Medical Sciences Academy, (2002) Vol. 15, No. 4, pp. 203-209. .
Refs: 16
ISSN: 0971-071X CODEN: JMSAE7
COUNTRY: India
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Oct 2003
Last Updated on STN: 30 Oct 2003
AB There has been a tremendous progress in the development of anti-retroviral agents in the recent past, keeping in mind that HIV/AIDS has become a global pandemic. These agents, however, only suppress the growth of the human **immunodeficiency** virus and have not been able to provide an effective cure for the disease. Though anti-retroviral drugs targeting all the different steps of replication, are being developed, the major groups of drugs, which are currently being used in clinical practice include reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). Among the RTIs are the nucleoside analogs (zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, delavirdine and efavirenz). The protease inhibitors include saquinavir, ritonavir, indinavir, amprinavir, nelfinavir and **lopinavir**. In the early 90s, therapy for HIV was generally limited to monotherapy with either zidovudine and later didanosine. However, the antiretroviral therapy changed dramatically in early 1996, probably because of an improved understanding of the pathogenesis of HIV infection, availability of tests that could measure plasma HIV RNA levels ("viral load"), development of new and more powerful drugs such as the protease inhibitors and early data suggesting that 3 drug regimens could - in theory - completely suppress viral replication. Therefore, aggressive highly active anti-retroviral regimen (HAART) is now th standard regime worldwide which includes at least three drugs from any of the above classes.
CT Medical Descriptors:
*highly active antiretroviral therapy

Human immunodeficiency virus infection: DT, drug therapy
Human immunodeficiency virus infection: EP, epidemiology
acquired immune deficiency syndrome: DT, drug therapy
acquired immune deficiency syndrome: EP, epidemiology
Human immunodeficiency virus
virogenesis
virus replication
monotherapy
pathogenesis
virus load
anorexia: SI, side effect
fatigue: SI, side effect
malaise: SI, side effect
myalgia: SI, side effect
nausea: SI, side effect
insomnia: SI, side effect
blood toxicity: SI, side effect
granulocytopenia: SI, side effect
anemia: SI, side effect
myopathy: SI, side effect
nail disease: SI, side effect
liver toxicity: SI, side effect
steatosis: SI, side effect
lactic acidosis: SI, side effect
diarrhea: SI, side effect
neuropathy: SI, side effect
chill: SI, side effect
fever: SI, side effect
rash: SI, side effect
abdominal pain: SI, side effect
muscle weakness: SI, side effect
pancreatitis: SI, side effect
hepatomegaly: SI, side effect
retina disease: SI, side effect
optic nerve disease: SI, side effect
peripheral neuropathy: SI, side effect
arthralgia: SI, side effect
ear infection: SI, side effect
nose infection: SI, side effect
pharyngitis: SI, side effect
neutropenia: SI, side effect
liver disease: SI, side effect
diabetes mellitus: SI, side effect
cyanocobalamin deficiency: SI, side effect
vertigo: SI, side effect
asthenia: SI, side effect
respiratory distress: SI, side effect
hypotension: SI, side effect
somnolence: SI, side effect
toxic epidermal necrolysis: SI, side effect
Stevens Johnson syndrome: SI, side effect
liver necrosis: SI, side effect
dermatitis: SI, side effect
paresthesia: SI, side effect
glucose intolerance: SI, side effect
hypercholesterolemia: SI, side effect
hypertriglyceridemia: SI, side effect
taste disorder: SI, side effect
crystalluria: SI, side effect

kidney colic: SI, side effect
nephrolithiasis: SI, side effect
hair disease: SI, side effect
skin disease: SI, side effect
hyperglycemia: SI, side effect
human
review

CT Drug Descriptors:
*antiretrovirus agent: AE, adverse drug reaction
*antiretrovirus agent: CB, drug combination
*antiretrovirus agent: IT, drug interaction
*antiretrovirus agent: DT, drug therapy
*antiretrovirus agent: PK, pharmacokinetics
RNA directed DNA polymerase inhibitor: AE, adverse drug reaction
RNA directed DNA polymerase inhibitor: CB, drug combination
RNA directed DNA polymerase inhibitor: IT, drug interaction
RNA directed DNA polymerase inhibitor: DT, drug therapy
RNA directed DNA polymerase inhibitor: PK, pharmacokinetics
RNA directed DNA polymerase inhibitor: PO, oral drug administration
proteinase inhibitor: CB, drug combination
proteinase inhibitor: DT, drug therapy
proteinase inhibitor: PK, pharmacokinetics
proteinase inhibitor: PD, pharmacology
zidovudine: AE, adverse drug reaction
zidovudine: IT, drug interaction
zidovudine: DT, drug therapy
zidovudine: PK, pharmacokinetics
zidovudine: PO, oral drug administration
didanosine: AE, adverse drug reaction
didanosine: CB, drug combination
didanosine: DT, drug therapy
didanosine: PK, pharmacokinetics
zalcitabine: AE, adverse drug reaction
zalcitabine: DT, drug therapy
zalcitabine: PK, pharmacokinetics
stavudine: AE, adverse drug reaction
stavudine: CB, drug combination
stavudine: DT, drug therapy
stavudine: PK, pharmacokinetics
lamivudine: AE, adverse drug reaction
lamivudine: CB, drug combination
lamivudine: DT, drug therapy
lamivudine: PK, pharmacokinetics
abacavir: AE, adverse drug reaction
abacavir: DT, drug therapy
abacavir: PK, pharmacokinetics
nevirapine: AE, adverse drug reaction
nevirapine: DT, drug therapy
nevirapine: PK, pharmacokinetics
delavirdine: AE, adverse drug reaction
delavirdine: IT, drug interaction
delavirdine: DT, drug therapy
delavirdine: PK, pharmacokinetics
efavirenz: AE, adverse drug reaction
efavirenz: DT, drug therapy
efavirenz: PK, pharmacokinetics
saquinavir: AE, adverse drug reaction
saquinavir: IT, drug interaction
saquinavir: DT, drug therapy

saquinavir: PK, pharmacokinetics
ritonavir: AE, adverse drug reaction
ritonavir: IT, drug interaction
ritonavir: DT, drug therapy
ritonavir: PK, pharmacokinetics
indinavir: IT, drug interaction
indinavir: DT, drug therapy
amprenavir: AE, adverse drug reaction
amprenavir: DT, drug therapy
amprenavir: PK, pharmacokinetics
nelfinavir: AE, adverse drug reaction
nelfinavir: IT, drug interaction
nelfinavir: DT, drug therapy
nelfinavir: PK, pharmacokinetics
lopinavir: AE, adverse drug reaction
lopinavir: DT, drug therapy
lopinavir: PK, pharmacokinetics
ganciclovir: IT, drug interaction
interferon: IT, drug interaction
flucytosine: IT, drug interaction
vincristine: AE, adverse drug reaction
vincristine: IT, drug interaction
vinblastine: IT, drug interaction
ethambutol: AE, adverse drug reaction
ethambutol: IT, drug interaction
pentamidine: AE, adverse drug reaction
pentamidine: IT, drug interaction
isoniazid: AE, adverse drug reaction
isoniazid: IT, drug interaction
cisplatin: AE, adverse drug reaction
cisplatin: IT, drug interaction
quinoline derived antiinfective agent: IT, drug interaction
tetracycline: IT, drug interaction
unindexed drug

RN (proteinase inhibitor) 37205-61-1; (zidovudine) 30516-87-1; (didanosine) 69655-05-6; (zalcitabine) 7481-89-2; (stavudine) 3056-17-5; (lamivudine) 134678-17-4, 134680-32-3; (abacavir) 136470-78-5, 188062-50-2; (nevirapine) 129618-40-2; (delavirdine) 136817-59-9; (efavirenz) 154598-52-4; (saquinavir) 127779-20-8, 149845-06-7; (ritonavir) 155213-67-5; (indinavir) 150378-17-9, 157810-81-6, 180683-37-8; (amprenavir) 161814-49-9; (nelfinavir) 159989-64-7, 159989-65-8; (lopinavir) 192725-17-0; (ganciclovir) 82410-32-0; (flucytosine) 2022-85-7; (vincristine) 57-22-7; (vinblastine) 865-21-4; (ethambutol) 10054-05-4, 1070-11-7, 3577-94-4, 74-55-5; (pentamidine) 100-33-4; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (tetracycline) 23843-90-5, 60-54-8, 64-75-5

L19 ANSWER 83 OF 93 EMBASE

ACCESSION NUMBER: 2003320111 EMBASE
TITLE: Clinical, immunological and virological response to different antiretroviral regimens in a cohort of HIV-2-infected patients.
AUTHOR: Van Der Ende M.E.; Prins J.M.; Brinkman K.; Keuter M.; Veenstra J.; Danner S.A.; Niesters H.G.M.; Osterhaus A.D.M.E.; Schutten M.
CORPORATE SOURCE: M.E. Van Der Ende, Univ. Hospital Rotterdam, Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, Netherlands. vanderende@inw2.azr.nl

SOURCE: AIDS, (2003) Vol. 17, No. SUPPL. 3, pp. S55-S61. .
Refs: 25
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Aug 2003
Last Updated on STN: 21 Aug 2003

AB Objective: To assess the clinical, **immunological** and virological response and the emergence of resistance towards antiretroviral therapy (ART) in a cohort of HIV-2-infected patients. Design: Observational study. Patients: HIV-2-infected patients residing in the Netherlands. Results: From 1995 to 2001 seven patients failed various ART regimens. The resistance mutations were analysed retrospectively. Development of mutations proved to be similar to that observed in HIV-1-infected patients, with the exception of a higher occurrence of the Q151M mutation within the reverse transcriptase gene. In a prospective study, comprising 13 consecutive naive HIV-2-infected patients, all patients achieved plasma HIV-2-RNA suppression below the detection limit (500 copies/ml). The antiretroviral regimen consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and indinavir, with a boosting dose of ritonavir; the median follow-up was 91 weeks. Two patients experienced a temporary virological rebound, while at the same time therapeutic drug monitoring showed sub-therapeutic plasma levels of indinavir. Conclusion: Sustained viral suppression in HIV-2-infected patients can be achieved using an antiretroviral regimen of two NRTIs and boosted indinavir or **lopinavir**. .COPYRGT. 2003 Lippincott Williams & Wilkins.

CT Medical Descriptors:
*Human immunodeficiency virus infection: DT, drug therapy
*Human immunodeficiency virus infection: ET, etiology
*highly active antiretroviral therapy
Human immunodeficiency virus 2
cohort analysis
immune response
virus virulence
Netherlands
virus mutation
gene mutation
drug mechanism
virus detection
antiviral activity
blood analysis
RNA analysis
follow up
drug dose regimen
rebound
drug monitoring
drug blood level
human
male
female
clinical article
clinical trial
controlled study

human cell
adult
article
priority journal
Drug Descriptors:
*RNA directed DNA polymerase inhibitor: CT, clinical trial
*RNA directed DNA polymerase inhibitor: CB, drug combination
*RNA directed DNA polymerase inhibitor: CR, drug concentration
*RNA directed DNA polymerase inhibitor: DT, drug therapy
*RNA directed DNA polymerase inhibitor: PD, pharmacology
*antiretrovirus agent: CT, clinical trial
*antiretrovirus agent: CB, drug combination
*antiretrovirus agent: CR, drug concentration
*antiretrovirus agent: DT, drug therapy
*antiretrovirus agent: PD, pharmacology
RNA directed DNA polymerase: EC, endogenous compound
virus RNA: EC, endogenous compound
indinavir: CT, clinical trial
indinavir: CB, drug combination
indinavir: CR, drug concentration
indinavir: DT, drug therapy
indinavir: PD, pharmacology
ritonavir: CT, clinical trial
ritonavir: CB, drug combination
ritonavir: CR, drug concentration
ritonavir: DT, drug therapy
ritonavir: PD, pharmacology
zidovudine: CT, clinical trial
zidovudine: CB, drug combination
zidovudine: CR, drug concentration
zidovudine: DT, drug therapy
zidovudine: PD, pharmacology
lamivudine: CT, clinical trial
lamivudine: CB, drug combination
lamivudine: CR, drug concentration
lamivudine: DT, drug therapy
lamivudine: PD, pharmacology
RN (RNA directed DNA polymerase) 37213-50-6, 9068-38-6; (indinavir) 150378-17-9, 157810-81-6, 180683-37-8; (ritonavir) 155213-67-5; (zidovudine) 30516-87-1; (lamivudine) 134678-17-4, 134680-32-3

L19 ANSWER 84 OF 93 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003123442 EMBASE
TITLE: [Optimization of protease inhibitors efficacy, using boosting activity].
OPTIMISATION DE L'EFFICACITE DES INHIBITEURS DE PROTEASE PAR «BOOSTING».
AUTHOR: Raffi F.
CORPORATE SOURCE: F. Raffi, CISIH, Hopital de l'Hotel-Dieu, 1, place Alexis-Ricordeau, 44093 Nantes Cedex, France
SOURCE: Medecine et Maladies Infectieuses, (1 Feb 2003) Vol. 33, No. SUPPL. 2, pp. 111s-116s. .
Refs: 15
ISSN: 0399-077X CODEN: MMAIB5
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 3 Apr 2003
Last Updated on STN: 3 Apr 2003

AB The introduction of Protease Inhibitors has added powerful therapeutic options among therapies against the infections caused by the human **immunodeficiency** virus. Nevertheless, the pharmacokinetic properties of these compounds with poor bioavailability and low residual concentrations may necessitate several daily intake of the drugs, with the inherent risk could be low observance, selection of resistant viral mutants and therapeutic failures. Boosting is a way to improve the pharmacokinetic of protease inhibitors by increasing the residual and maximal concentrations. But, the risk could be to approach the plasmatic level of toxicity of the drugs and to increase the occurrence of drugs interactions. Boosting with low doses of ritonavir is particularly interesting with saquinavir, **lopinavir**, indinavir and amprenavir, permitting to significantly improve their residual concentrations. In an other hand, we observe a higher rate of clinical and metabolic side effects under the association of protease inhibitors and ritonavir.

CT Medical Descriptors:
drug efficacy
drug activity
Human immunodeficiency virus
Human immunodeficiency virus infection: DT, drug therapy
drug bioavailability
drug blood level
drug tolerability
risk factor
side effect: SI, side effect
metabolic disorder: SI, side effect
nephrolithiasis: SI, side effect
diarrhea: SI, side effect
asthenia: SI, side effect
gastroesophageal reflux: SI, side effect
nausea: SI, side effect
hyperglycemia: SI, side effect
hypercholesterolemia: SI, side effect
hypertriglyceridemia: SI, side effect
hyperamylasemia: SI, side effect
human
review
Drug Descriptors:
*proteinase inhibitor: AE, adverse drug reaction
*proteinase inhibitor: CR, drug concentration
*proteinase inhibitor: IT, drug interaction
*proteinase inhibitor: DT, drug therapy
*proteinase inhibitor: PK, pharmacokinetics
ritonavir: AE, adverse drug reaction
ritonavir: CR, drug concentration
ritonavir: IT, drug interaction
ritonavir: DT, drug therapy
saquinavir: AE, adverse drug reaction
saquinavir: CR, drug concentration
saquinavir: IT, drug interaction
saquinavir: DT, drug therapy

lopinavir: AE, adverse drug reaction
lopinavir: CR, drug concentration
lopinavir: IT, drug interaction
lopinavir: DT, drug therapy
indinavir: AE, adverse drug reaction
indinavir: CR, drug concentration
indinavir: IT, drug interaction
indinavir: DT, drug therapy
amprenavir: AE, adverse drug reaction
amprenavir: CR, drug concentration
amprenavir: IT, drug interaction
amprenavir: DT, drug therapy
RN (proteinase inhibitor) 37205-61-1; (ritonavir) 155213-67-5; (saquinavir) 127779-20-8, 149845-06-7; (lopinavir) 192725-17-0; (indinavir) 150378-17-9, 157810-81-6, 180683-37-8; (amprenavir) 161814-49-9

L19 ANSWER 85 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-069524 [07] WPIX
CROSS REFERENCE: 2004-440464 [41]
DOC. NO. NON-CPI: N2004-055882
DOC. NO. CPI: C2004-028928
TITLE: Transmucosal composition useful for the transmucosal delivery of drugs comprises non-ionizable glycol derivative and pharmaceutical agent.
DERWENT CLASS: A96 B05 B07 P34
INVENTOR(S): LIU, J H; PAULETTI, G M; RITSCHELL, W A; GIOVANNI, P M; RITSCHEL, W A
PATENT ASSIGNEE(S): (LIUJ-I) LIU J H; (PAUL-I) PAULETTI G M; (RITS-I) RITSCHELL W A; (UMDU-N) UMD INC
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003219472	A1	20031127	(200407)*		16<--
WO 2003099264	A1	20031204	(200407)	EN	<--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003233653	A1	20031212	(200443)		<--
EP 1509209	A1	20050302	(200517)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
NO 2004005140	A	20050222	(200530)		
BR 2003011530	A	20050510	(200533)		
JP 2005531570	W	20051020	(200569)		31
MX 2004011584	A1	20050401	(200571)		
CN 1662228	A	20050831	(200611)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003219472	A1 Provisional	US 2002-382644P	20020523
		US 2003-444634	20030522

WO 2003099264	A1	WO 2003-US16313	20030522
AU 2003233653	A1	AU 2003-233653	20030522
EP 1509209	A1	EP 2003-729092	20030522
		WO 2003-US16313	20030522
NO 2004005140	A	WO 2003-US16313	20030522
		NO 2004-5140	20041125
BR 2003011530	A	BR 2003-11530	20030522
		WO 2003-US16313	20030522
JP 2005531570	W	WO 2003-US16313	20030522
		JP 2004-506788	20030522
MX 2004011584	A1	WO 2003-US16313	20030522
		MX 2004-11584	20041122
CN 1662228	A	CN 2003-814727	20030522

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003233653	A1 Based on	WO 2003099264
EP 1509209	A1 Based on	WO 2003099264
BR 2003011530	A Based on	WO 2003099264
JP 2005531570	W Based on	WO 2003099264
MX 2004011584	A1 Based on	WO 2003099264

PRIORITY APPLN. INFO: US 2002-382644P 20020523; US 2003-444634 20030522

AB US2003219472 A UPAB: 20060214
NOVELTY - A transmucosal composition (C1) comprises non-ionizable glycol derivative (a1) (0.01-60, preferably 10-15, especially 15 weight%) and pharmaceutical agent (a2) (0.001-2000 mg) having log p of greater than or less than 2.5.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for transmucosal delivery of drugs involving contacting the vaginal, nasal or buccal mucosa with a composition (C2) containing a polar pharmaceutical agent (a3) having log p of less than 2.5 and (a1) (0.01-60 weight%) selected from glycol ester, glycol ether and/or glycerol esters.

USE - For transmucosal delivery of a pharmaceutical agent or drugs (claimed); for cryoprotecting of cells, tissues, organs and embryos; for long-term preservation of cell or embryos.

ADVANTAGE - The composition promotes and permits transmucosal drug delivery through a nasal, buccal, and vaginal mucosa into the general blood circulation. The composition is non-invasive, requires no assistance by medical personnel or visit to the doctor's office, eliminates the need for administration of excessive doses of the drugs needed for administration of excessive doses of the drug needed for the oral delivery and more convenient, practical and economical. The composition bypasses the gastrointestinal tract absorption, liver metabolism and kidney deactivation and delivers the drug directly to the systemic blood circulation.

Dwg.0/4

L19 ANSWER 86 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-902656 [82] WPIX
DOC. NO. CPI: C2003-256176
TITLE: Composition for treating human immune deficiency virus infection, contains immunomodulatory peptide and antiretroviral agent.
DERWENT CLASS: B04
INVENTOR(S): BUELOW, R; DANDEKAR, S; IYER, S

PATENT ASSIGNEE(S): (SANG-N) SANGSTAT MEDICAL CORP; (BUEL-I) BUELOW R; (DAND-I) DANDEKAR S; (IYER-I) IYER S
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003061602	A2	20030731	(200382)*	EN	65<--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003210659	A1	20030902	(200422)		<--
US 2004127422	A1	20040701	(200444)		
EP 1525216	A2	20050427	(200529)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003061602	A2	WO 2003-US2275	20030124
AU 2003210659	A1	AU 2003-210659	20030124
US 2004127422	A1 Provisional	US 2002-351925P	20020124
		US 2003-351608	20030124
EP 1525216	A2	EP 2003-732095	20030124
		WO 2003-US2275	20030124

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003210659	A1 Based on	WO 2003061602
EP 1525216	A2 Based on	WO 2003061602

PRIORITY APPLN. INFO: US 2002-351925P 20020124; US 2003-351608 20030124

AB WO2003061602 A UPAB: 20031223
NOVELTY - Composition (A) for treating HIV infection comprises an immunomodulatory peptide (I) and at least one anti-retroviral agent (II).

ACTIVITY - Anti-HIV; Immunomodulatory.

The compound Arg-(nL)3-Arg-(nL)3-Gly-Tyr (Ia) was administered at 2 mg/kg, 3 times a week in drinking water, to rhesus macques infected with simian immune deficiency virus, together with 9-R-(2-phosphonomethoxypropyl)adenine (PMPA) at 30 mg/kg, intravenously. After 16 weeks, the log (viral RNA copies/ml of plasma) was 1-1.5 for animals given both drugs and 3-4 for those given only PMPA. The combined therapy also increased the population of CD4+ and CD4+CD8+ cells in the jejunal mucosa.

MECHANISM OF ACTION - (II) modulates activity of T cells and/or inhibits production of inflammatory cytokines (and this antiinflammatory action may stabilize the intestinal mucosa); (I) inhibits viral enzymes, co-receptors or viral adsorption.

USE - (A) is used to treat HIV-infected subjects, particularly for treating gastrointestinal complications or inflammatory reactions associated with HIV.

ADVANTAGE - (A) increases the levels of CD4+ and CD4+CD8+ T cells, so provides rapid and sustainable restoration and normalization of the immune system in gut-associated lymphoid tissue. There is synergism between the effects of (I) and (II).
Dwg.0/9

L19 ANSWER 87 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-875322 [81] WPIX
CROSS REFERENCE: 2001-597217 [67]; 2002-121422 [16]; 2005-417059 [42]
DOC. NO. CPI: C2003-247246
TITLE: New crystalline or substantially pure crystalline hydrate, solvated or non-solvated form of human **immunodeficiency** virus protease inhibitor, **lopinavir**, useful for the treatment of HIV infection.
DERWENT CLASS: B03
INVENTOR(S): CHEMBURKAR, S; DICKMAN, D A; FORT, J J; HENRY, R F; LECHUGA-BALLESTEROS, D; NIU, Y; PORTER, W
PATENT ASSIGNEE(S): (CHEM-I) CHEMBURKAR S; (DICK-I) DICKMAN D A; (FORT-I) FORT J J; (HENR-I) HENRY R F; (LECH-I) LECHUGA-BALLESTEROS D; (NIUY-I) NIU Y; (PORT-I) PORTER W; (ABBO) ABBOTT LAB
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003191313	A1	20031009	(200381)*		46<--
US 6864369	B2	20050308	(200518)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2003191313	A1	Provisional	US 2000-193573P	20000330
		Div ex	US 2001-793536	20010227
			US 2003-387175	20030312
US 6864369	B2	Provisional	US 2000-193573P	20000330
		Div ex	US 2001-793536	20010227
			US 2003-387175	20030312

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 6864369	B2 Div ex	US 6608198

PRIORITY APPLN. INFO: US 2000-193573P 20000330; US 2001-793536 20010227; US 2003-387175 20030312

AB US2003191313 A UPAB: 20050704
NOVELTY - A crystalline or substantially pure crystalline hydrate, solvated or non-solvated form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl)amino-1,6-diphenylhexane (lopinavir) is new.
ACTIVITY - Anti-HIV.
No biological data available.
MECHANISM OF ACTION - HIV protease inhibitor.
USE - The crystalline form of lopinavir is useful for the preparation

of pharmaceutical compositions to inhibit HIV infection.
ADVANTAGE - The crystalline form of lopinavir is free from impurities, or has a greatly reduced amount of impurities.
Dwg.0/31

L19 ANSWER 88 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-559019 [52] WPIX
DOC. NO. CPI: C2003-150657
TITLE: Use of human immunodeficiency virus-protease inhibitor for the mitigation/treatment of an inflammatory response in a patient e.g. arthritis.
DERWENT CLASS: B04 B05 D16
INVENTOR(S): ARDITI, M; EQUILS, O
PATENT ASSIGNEE(S): (CEDA-N) CEDARS SINAI MEDICAL CENT
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003051361	A1	20030626	(200352)*	EN	22<--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
US 2003138423	A1	20030724	(200352)		<--
AU 2002346594	A1	20030630	(200420)		<--
EP 1453504	A1	20040908	(200459)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
JP 2005511767	W	20050428	(200530)		24

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003051361	A1	WO 2002-US38259	20021127
US 2003138423	A1 Provisional	US 2001-340507P	20011214
		US 2002-306000	20021127
AU 2002346594	A1	AU 2002-346594	20021127
EP 1453504	A1	EP 2002-784665	20021127
		WO 2002-US38259	20021127
JP 2005511767	W	WO 2002-US38259	20021127
		JP 2003-552294	20021127

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002346594	A1 Based on	WO 2003051361
EP 1453504	A1 Based on	WO 2003051361
JP 2005511767	W Based on	WO 2003051361

PRIORITY APPLN. INFO: US 2001-340507P 20011214; US 2002-306000 20021127
AB WO2003051361 A UPAB: 20030813
NOVELTY - Administration of an HIV-protease inhibitor (A) to mitigate an inflammatory response.

ACTIVITY - Antibacterial; Antiarthritic; Antirheumatic; Osteopathic; Antiinflammatory; Antipsoriatic; Antigout; Gastrointestinal-Gen.; Antiulcer; Neuroprotective; Nephrotropic; Immunosuppressive; Dermatological; Cardiant; Anti-HIV; Virucide.

MECHANISM OF ACTION - HIV-1 protease inhibitor; NF-kB cell signal transduction modulator.

A luciferase activity was determined using nelfinavir (as HIV-1 protease inhibitor; as test compound) against immortalized human dermal endothelial cells (HMEC) at concentrations 1, 3 and 6 mu g/ml before and at the time of LPS (lipopolysaccharide) stimulation. The % NF-kB and % HIV-L TR luciferase activities of the test compound was found to be 50, 35 and 20 at 1, 3 and 6 mg/ml (dose dependent manner) and 110, 100 and 100; 80, approx. 80 and approx. 80 and 40, 60 and 40 at 0.5, 2 and 4 mu g/ml after 30, 60 and 120 minutes (time dependent manner) respectively. Thus the pretreatment with the test compound inhibited LPS-induced NF-kB activation in both a dose-dependent and time-dependent manner.

USE - In the mitigation/treatment of an inflammatory response in a patient/a disease condition including an inflammatory response or disease condition in a patient (where NF-kB cell signal transduction is hindered) e.g. sepsis, severe sepsis, arthritis, rheumatoid arthritis, osteoarthritis, inflammatory arthritis, psoriatic arthritis, gout, an inflammatory condition of the gastrointestinal tract, inflammatory bowel disease, ulcerative colitis, Crohn's disease, a neurologic inflammatory condition, meningitis, inflammatory myocarditis, glomerulonephritis, an autoimmune disease and lupus (all claimed); HIV and AIDS; in the treatment of cellular inflammatory or abnormally exaggerated immune response.

ADVANTAGE - (A) down-modulate NF-kB cell signal transduction affects the NF-kB signaling pathway by down-modulating the enzymatic digestion of an IkB protein/NF-kB complex into its constituent parts which reduces the amount of free NF-kB that translocates from cell cytoplasm to the cell nucleus in response to a cell signal that would otherwise cause NF-kB to initiate transcription according with an immune or inflammatory response; partially hinders the phosphorylation and proteolysis that affect the enzymatic digestion.

Dwg.0/9

L19 ANSWER 89 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-140484 [13] WPIX
CROSS REFERENCE: 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37];
1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05];
2001-244406 [25]; 2001-607195 [69]; 2001-616242 [71];
2002-215899 [27]; 2002-617759 [66]; 2003-058513 [05];
2003-140439 [13]; 2003-201244 [19]; 2003-229207 [22];
2003-587106 [55]; 2003-671816 [63]; 2003-679850 [64];
2003-679873 [64]; 2003-679876 [64]; 2003-679877 [64];
2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65];
2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65];
2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65];
2003-697557 [66]; 2003-697604 [66]; 2003-697605 [66];
2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66];
2003-697611 [66]; 2003-697612 [66]; 2003-697624 [66];
2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67];
2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68];
2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69];
2003-854127 [79]; 2003-901032 [82]; 2004-031273 [03];
2004-032029 [03]; 2004-053455 [05]; 2004-247781 [23];
2004-440369 [41]; 2004-766879 [75]; 2005-012649 [01];
2005-040107 [04]; 2005-090672 [10]; 2005-091819 [10];
2005-112870 [12]; 2005-112874 [12]; 2005-163247 [17];

2005-213083 [22]; 2005-254128 [26]; 2005-254129 [26]; 2005-261673 [27]; 2005-306364 [31]; 2005-331064 [34]; 2005-331166 [34]; 2005-333508 [34]; 2005-345053 [35]; 2005-347065 [35]; 2005-356234 [36]; 2005-356235 [36]; 2005-356236 [36]; 2005-366846 [37]; 2005-417025 [42]; 2005-417026 [42]; 2005-456992 [46]; 2005-457526 [46]; 2005-457527 [46]; 2005-457799 [46]; 2005-466131 [47]; 2005-494869 [50]; 2005-494870 [50]; 2005-496858 [50]; 2005-505468 [51]; 2005-505469 [51]; 2005-512269 [52]; 2005-521407 [53]; 2005-532291 [54]; 2005-541386 [55]; 2005-554284 [56]; 2005-581759 [59]; 2005-581760 [59]; 2005-581761 [59]; 2005-604644 [62]; 2005-604645 [62]; 2005-604649 [62]; 2005-638520 [65]; 2005-648281 [66]; 2005-664178 [68]; 2005-712679 [73]; 2005-746882 [76]; 2005-746889 [76]; 2005-746891 [76]; 2005-746892 [76]; 2005-746893 [76]; 2005-748252 [77]; 2005-768338 [78]; 2005-769550 [78]; 2006-009410 [01]; 2006-037938 [04]; 2006-037965 [04]; 2006-055966 [06]; 2006-056068 [06]; 2006-134230 [14]; 2006-134231 [14]; 2006-135499 [14]; 2006-190836 [20]

DOC. NO. CPI: C2003-035699

TITLE: Novel short interfering RNA and enzymatic nucleic acid useful for treating cancer, modulates the expression of a nucleic acid encoding HER2, K-Ras, H-Ras, N-Ras, and human deficiency virus sequences.

DERWENT CLASS: A96 B02 B04 B05 C02 C03 D16

INVENTOR(S): MCSWIGGEN, J; BEIGELMAN, L; MACEJAK, D

PATENT ASSIGNEE(S): (RIBO-N) RIBOZYME PHARM INC; (SIRN-N) SIRNA THERAPEUTICS INC; (MCSW-I) MCSWIGGEN J

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002097114	A2	20021205	(200313)*	EN	185<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2003105051	A1	20030605	(200339)		<--
US 2003124513	A1	20030703	(200345)		<--
US 2003153521	A1	20030814	(200355)		<--
EP 1390472	A2	20040225	(200415)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
AU 2002305729	A1	20021209	(200452)		<--
US 2005191618	A1	20050901	(200557)		
AU 2002305729	A8	20051013	(200611)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002097114	A2	WO 2002-US16840	20020529
US 2003105051	A1 Provisional	US 2001-296249P	20010606
		US 2002-163552	20020606

US 2003124513	A1	Provisional	US 2001-294140P	20010529
			US 2002-157580	20020529
US 2003153521	A1	Provisional	US 2001-318471P	20010910
			US 2002-238700	20020910
EP 1390472	A2		EP 2002-734572	20020529
			WO 2002-US16840	20020529
AU 2002305729	A1		AU 2002-305729	20020529
US 2005191618	A1	Provisional	US 2001-292217P	20010518
		Provisional	US 2001-294140P	20010529
		Provisional	US 2001-306883P	20010720
		Provisional	US 2001-311865P	20010813
		Provisional	US 2002-358580P	20020220
		Provisional	US 2002-362016P	20020306
		Provisional	US 2002-363124P	20020311
		Provisional	US 2002-374722P	20020423
		CIP of	WO 2002-US15876	20020517
		CIP of	US 2002-157580	20020529
		Provisional	US 2002-386782P	20020606
		Provisional	US 2002-398036P	20020723
		CIP of	US 2002-225023	20020821
		Provisional	US 2002-406784P	20020829
		Provisional	US 2002-408378P	20020905
		Provisional	US 2002-409293P	20020909
		Provisional	US 2003-440129P	20030115
		CIP of	WO 2003-US5028	20030220
		CIP of	WO 2003-US5190	20030220
		CIP of	WO 2003-US5346	20030220
		CIP of	US 2003-420194	20030422
		CIP of	WO 2003-US12626	20030422
		CIP of	US 2003-427160	20030430
		CIP of	US 2003-444853	20030523
		CIP of	US 2003-693059	20031023
		CIP of	US 2003-720448	20031124
		CIP of	US 2003-727780	20031203
		CIP of	US 2004-757803	20040114
		Provisional	US 2004-543480P	20040210
		CIP of	US 2004-780447	20040213
		CIP of	US 2004-826966	20040416
		Cont of	WO 2004-US13456	20040430
		Cont of	WO 2004-US16390	20040524
			US 2004-923473	20040820
AU 2002305729	A8		AU 2002-305729	20020529

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1390472	A2	Based on	WO 2002097114
AU 2002305729	A1	Based on	WO 2002097114
AU 2002305729	A8	Based on	WO 2002097114

PRIORITY APPLN. INFO: US 2001-318471P 20010910; US
2001-294140P 20010529; US
2001-296249P 20010606; US
2002-163552 20020606; US
2002-157580 20020529; US
2001-292217P 20010518; US
2001-306883P 20010720; US
2001-311865P 20010813; US

2002-358580P	20020220; US
2002-362016P	20020306; US
2002-363124P	20020311; US
2002-374722P	20020423; WO
2002-US15876	20020517; US
2002-386782P	20020606; US
2002-398036P	20020723; US
2002-225023	20020821; US
2002-406784P	20020829; US
2002-408378P	20020905; US
2002-409293P	20020909; US
2003-440129P	20030115; WO
2003-US5028	20030220; WO
2003-US5190	20030220; WO
2003-US5346	20030220; US
2003-420194	20030422; WO
2003-US12626	20030422; US
2003-427160	20030430; US
2003-444853	20030523; US
2003-693059	20031023; US
2003-720448	20031124; US
2003-727780	20031203; US
2004-757803	20040114; US
2004-543480P	20040210; US
2004-780447	20040213; US
2004-826966	20040416; WO
2004-US13456	20040430; WO
2004-US16390	20040524; US
2004-923473	20040820

AB WO 200297114 A UPAB: 20060323
NOVELTY - A short interfering RNA (siRNA) nucleic acid molecule (I) or an enzymatic nucleic acid molecule (II), that modulates expression of a nucleic acid molecule encoding HER2, K-Ras, H-Ras, N-Ras, human deficiency virus (HIV) or a component of HIV, is new.

DETAILED DESCRIPTION - (I) and (II) modulates the expression of a nucleic acid encoding HER2, K-Ras, H-Ras, N-Ras, HIV or a component of HIV. (I) comprises a sequence complementary to any of 3406 15-20 nucleotide sequences (S1), given in the specification. (II) comprises a sequence complementary to one of 3393 30 nucleotide sequences (S2) given in the specification. It comprises at least one binding arm, where the binding arms comprises a sequence complementary to S1. (II) which modulates expression of a nucleic acid encoding HIV or a component of HIV, is in an inozyme, G-cleaver, zinzyme or amberzyme configuration.

INDEPENDENT CLAIMS are also included for the following:

(1) an expression vector (III) comprising (I) and (II) in a manner that allows expression of the nucleic acid molecule;

(2) a mammalian cell (IV) comprising (I), (II), and (III); and

(3) a pharmaceutical composition (V) comprising (I), (II), and a carrier.

ACTIVITY - Cytostatic; Anti-HIV; Antirheumatic.

No biological data is given.

MECHANISM OF ACTION - Modulator of expression of HER2, K-Ras, H-Ras, N-Ras, and HIV.

USE - (I) and (II) are useful for reducing HER2, K-Ras, H-Ras, and HIV activity in a cell, by contacting the cell with (I) or (II) under conditions suitable for the reduction of HER2, K-Ras, H-Ras, and HIV activity, and also for treating breast, ovarian, colorectal, lung, prostate, bladder, or pancreatic cancer. (I) and (II) are also useful for treating a condition associated with the level of HER2, K-Ras, H-Ras, and

HIV, by contacting the cells with (I) or (II) under conditions suitable for treatment. The method further involves administering one or more therapies chosen from monoclonal **antibody** (Mab) therapy, chemotherapy, radiation therapy, and analgesic therapy, where Mab is herceptin (trastuzumab). The chemotherapy is selected from paclitaxel (taxol), docetaxel, cisplatin, methotrexate, cyclophosphamide, doxorubin, fluorouracil, carboplatin, edatrexate, gemcitabine, and vinorelbine. When treating a subject having a condition associated with level of HIV with (I) or (II), the method involves administering one or more drug therapies chosen from antiviral therapy, Mab therapy, chemotherapy, radiation therapy, analgesic therapy, and anti-inflammatory therapy. The antiviral therapy is selected from treatment with 3'-azido-3'-deoxythymidine (AZT), ddC, ddI, d4T, 3TC, ribavirin, delvaridine, nevirapine, efravirenz, ritonavir, saquinivir, indinavir, amprenivir, nelfinavir, and **lopinavir**. (I) and/or (II) is useful for cleaving RNA having HER2, K-Ras, H-Ras, and HIV gene, by contacting (I) and/or (II) with RNA under conditions suitable for cleavage, where the cleavage is carried out in the presence of a divalent cation, especially Mg2+. (I) and (II) are useful for treating AIDS, or AIDS related condition, where the AIDS related condition is Kaposi's sarcoma, lymphoma, cervical cancer, squamous cell carcinoma, cardiac myopathy, rheumatic disease, or opportunistic infection. (I) and (II) are also useful for administering to a cell, by contacting the cell with (I) or (II), where the cell is a human cell. administration is in presence of a delivery reagent such as a lipid, or a liposome. The lipid is a cationic lipid, or a phospholipid. (I) and (II) are further useful for treating cancer, HIV infection, and AIDS. (All claimed.) (I) and (II) are useful as diagnostic tool to examine genetic drift and mutations within the diseased cells or to detect the presence of HER2, or Ras RNA in a cell. (I) and (II) are also useful to modulate gene expression of target genes in bacterial, microbial, fungal, viral, and eukaryotic systems including plant or mammalian cells. (II) is useful to identify wild-type and mutant RNA present in the sample.

DESCRIPTION OF DRAWING(S) - The drawing shows a DNAzyme motif.

Dwg.4/4

L19 ANSWER 90 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-706847 [76] WPIX
DOC. NO. CPI: C2002-200428
TITLE: Composition useful in the treatment of cancer comprises at least one of incensole or furanogermacrens.
DERWENT CLASS: A96 B05
INVENTOR(S): SHANAHAN-PRENDERGAST, E
PATENT ASSIGNEE(S): (SHAN-I) SHANAHAN-PRENDERGAST E
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002053138	A2	20020711	(200276)*	EN	68<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
EP 1351678	A2	20031015	(200368)	EN	<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

AU 2002219472 A1 20020716 (200427) <--
US 2004092583 A1 20040513 (200432)
AU 2002219472 A8 20050915 (200569)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002053138	A2	WO 2002-IE1	20020102
EP 1351678	A2	EP 2002-727007	20020102
		WO 2002-IE1	20020102
AU 2002219472	A1	AU 2002-219472	20020102
US 2004092583	A1	WO 2002-IE1	20020102
		US 2004-250535	20040102
AU 2002219472	A8	AU 2002-219472	20020102

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1351678	A2 Based on	WO 2002053138
AU 2002219472	A1 Based on	WO 2002053138
AU 2002219472	A8 Based on	WO 2002053138

PRIORITY APPLN. INFO: IE 2001-2 20010102

AB WO 200253138 A UPAB: 20021125

NOVELTY - A composition comprises at least one of incensole (I) or furanogermacrens (II), their derivative, metabolite, analog and/or mimic molecule with an additive, a diluent, a carrier, an excipient, or their salts.

DETAILED DESCRIPTION - A composition comprises at least one of incensole (I) or furanogermacrens (II), their derivative, metabolite, analog and/or mimic molecule with an additive, a diluent, a carrier, an excipient, or their salts.

ACTIVITY - Antidiabetic; Cerebroprotective; Antiarthritic; Cytostatic; Virucide; Immunosuppressive; Antifungal; Protozoacide; Amebicide; Antibacterial; Vulnerary; Immunomodulator; Antiinflammatory; Neuroprotective; Antiparasitic; Ophthalmological; Keratolytic; Antidiarrheic; Antiasthmatic; Dermatological; Neuroprotective; Hepatotropic.

MECHANISM OF ACTION - Tumor cell growth inhibitor; Endogenous hsp level enhancer; Endogenous precursor dendritic cell level enhancer.

In vitro cytotoxic activity of extracts containing high concentration of incensole and furanogermacren mixture were determined in human melanoma cancer cell line by MTT colonogenic assay. Human tumor (melanoma) cell lines were grown in RPMI 1640 supplemented with 10 % fetal calf serum and L-glutamine (2 mM). The cells were kept at 5% CO2 and 37 deg. C and passaged routinely, washed and counted. The cologenic assay was performed according to a modified two-layered soft agar assay, where the bottom layer consisted of Iscove's MDM (0.2 ml) with 20% fetal calf serum and 0.75 % agar.

After 24 hours, drugs were added in additional RPMI medium (0.2 ml) with 5-fluorouracil as positive control (100, 300, and 1000 micro g/ml). Cultures were incubated at 5% CO2 and 37 deg. C in a humidified atmosphere for 5-6 days until formation of colonies with diameter of 50 micro m (counts performed with automated image analysis system). Vital colonies were stained with sterile aqueous solution of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride (1 mg/ml) 24 hours prior to evaluation. The IC50 value for (A) was found to be 0.8 micro m/ml.

USE - This composition is used in the manufacture of medicament for the treatment of a mammal, preferably a neonate, suffering from neoplasia, especially in the sensitization of a resistant neoplasia such as precancerous lesion including syndromes represented by abnormal neoplastic and/or dysplastic, changes of tissue comprising precancerous growths in colonic, breast, renal, central nervous, gastric, or lung tissues, or conditions such as dysplastic nevus syndrome, a precursor to malignant melanoma of the skin, dysplastic nevus syndromes, polyposis syndromes, colonic polyps, precancerous lesions of the cervix (including cervical dysplasia), prostatic dysplasia, bronchial dysplasia, breast, bladder and/or skin and related conditions (actinic keratosis), whether the lesions are clinically identifiable or not, prostate, colon, small and large cell lung cancer, lung adenocarcinoma, epidermoid lung cancer, melanoma (including amelanotic subtypes), renal cell carcinoma, gastric carcinoma, cancers of the central nervous system including brain tumors, neuroblastomas, gastric carcinoma, breast, ovarian, testicular, esophageal, stomach, liver, cervical, adrenal, oral, mucosal, bladder or pancreatic cancer, lymphoma, Hodgkin's disease, sarcomas, hematopoeitic cell cancers such as B cell leukaemia/lymphomas, myelomas, T-cell or small cell leukemias/lymphomas, null cell, sezary, monacytic, myelomonocytic and hairy cell leukemias; neoplasias in the form of tumor containing epidermoid and myeloid tumor, acute or chronic, nonsmall cell, squamous or solid; immunodysregulatory condition caused by viral, extra- or intracellular bacterial, fungal, yeast, extra- or intracellular parasite infection, protozoan parasite, multicellular parasite, autoimmune disease, immunosuppressive therapy, chemotherapy, anti-infective agent therapy, wound, burn, the presence of an immunosuppressive molecule and/or gastrointestinal irritation, due to a DNA or RNA virus infection, a parasite infection selected from Trypanosoma (including Trypanosoma cruz, Trypanosoma brucei, Trypanosoma gambiense, Trypanosoma rhodesiense), Plasmodium (Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, Plasmodium berghei), Cryptosporidium, Entamoeba (including Entamoeba histolytica), Balantidium (including Balantidium coli), Leishmania (including Leishmania brazilienis, Leishmania mexicana, Leishmania donovani, Leishmania tropica), Pneumocystis (including Pneumocystis carinii), Trichomoniasis (including Trichomoniasis vaginalis) or Toxoplasma infection (including Toxoplasma gondii); a Mycoplasma, Listeria or Mycobacterium infection; Streptococcus, Staphylococcus, Vibrio, Salmonella or Shigella infection, enterotoxigenic, enteropathogenic, enteroinvasive or enterohemorrhagic E. coli infection, Yersinia, Campylobacter, Pseudomonas, Borrelia, Legionella or Hemophilus infection; pulmonary Aspergillosis, mucosal or oropharyngealcandidiasis and juvenile paracoccidiomyosis; Candida or Cryptococcus infection; systemic lupus erythematosus, arthritis, asthma, and diabetes; adriamycin treatment, cisplatin treatment, mitomycin C treatment, amphoteracin B treatment; gamma-radiation treatment; nucleoside analog treatment for viral infection or for cancer; surgical and accidental wounds, septic shock caused by surgery; cyclosporin treatment and corticosteroid treatment; irritable bowel treatment, Crohn's disease, wasting syndrome, cachexia, Motor Neuron disease, multiple sclerosis, inflammatory bowel disease, respiratory distress syndrome, chronic diarrhea; cancer; cirrhosis; and/or gram positive multi-drug resistant bacteria. The DNA virus infection or the RNA virus infection includes retrovirus, togavirus, flavivirus, rubivirus, pestivirus, lipid envelope virus, flovirus, picornavirus, rhinovirus, coronavirus, respiratory syncytial virus, poliovirus, parainfluenza virus, influenza virus, hantavirus, adeno-associated virus, measles virus, poxvirus, filovirus, human papilloma virus and animal papilloma virus infection (claimed).

ADVANTAGE - The composition allows the patient to suspend therapy for

periods without the worry of inactivity of the drug resulting from the development of resistant cells. The composition exhibits a potent immuno-modulatory effects, provides enhanced antitumor effect and prevents the development of metastasis, overcomes multi drug resistant tumors, and can be administered separately or as a cocktail. The composition regulates immuno responses, and treats neoplasia with minimal toxic side effects unlike the high toxicity associated with standard chemotherapeutic agents. The composition further enhances endogenous hsp levels, and endogenous precursor dendritic cell levels, which results in enhanced immunosurvillence. The composition also upregulates natural killer cells and improves presentation of antigenic peptides to the cytotoxic T cells. Dwg.0/0

L19 ANSWER 91 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-471407 [50] WPIX
DOC. NO. NON-CPI: N2002-372140
DOC. NO. CPI: C2002-134046
TITLE: Predicting resistance of a disease to therapy e.g. antiviral therapy, by determining biological cut-off values from mean and standard deviation values of fold resistance of patient's sample relative to reference sample.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): HARRIGAN, R P; HERTOGS, K; LARDER, B
PATENT ASSIGNEE(S): (VIRC-N) VIRCO NV; (VIRC-N) VIRCO BVBA; (HARR-I) HARRIGAN R P; (HERT-I) HERTOGS K; (LARD-I) LARDER B
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002033402	A2	20020425	(200250)*	EN	22<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2002012344	A	20020429	(200255)		<--
EP 1340075	A2	20030903	(200365)	EN	<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2004033489	A1	20040219	(200414)		
JP 2004511800	W	20040415	(200426)		40

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002033402	A2	WO 2001-EP12337	20011022
AU 2002012344	A	AU 2002-12344	20011022
EP 1340075	A2	EP 2001-980518	20011022
		WO 2001-EP12337	20011022
US 2004033489	A1	WO 2001-EP12337	20011022
		US 2003-399412	20030417
JP 2004511800	W	WO 2001-EP12337	20011022
		JP 2002-536538	20011022

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002012344	A Based on	WO 2002033402
EP 1340075	A2 Based on	WO 2002033402
JP 2004511800	W Based on	WO 2002033402

PRIORITY APPLN. INFO: US 2000-241836P 20001020; US 2003-399412 20030417

AB WO 200233402 A UPAB: 20020807
NOVELTY - Predicting resistance of a disease to a therapy, comprises determining sensitivities of a patient sample (S1) and reference sample (S2) for a therapy, determining patient fold resistance (PFR) from quotient of sensitivity obtained for S1 over sensitivity obtained for S2, and predicting resistance of a disease toward a therapy by determining whether PFR is above a cut-off fold resistance value.

DETAILED DESCRIPTION - Predicting (M1) resistance of a disease to a therapy, comprises determining sensitivities of a patient sample (S1) and reference sample (S2) for a therapy, determining patient fold resistance (PFR) from quotient of sensitivity obtained for S1 over sensitivity obtained for S2, and predicting resistance of a disease toward a therapy by determining whether PFR is above a cut-off fold resistance value. (M1) comprises determining the sensitivity of S1 and S2 for at least one therapy, determining PFR from the quotient of the sensitivity obtained for S1 over the sensitivity obtained for S2, predicting resistance of a disease toward at least one therapy by determining whether PFR is above a cut-off fold resistance value, where the cut-off fold resistance value is determined from the mean and standard deviation of a distribution of PFR values for the at least therapy determined for a group of patient.

An INDEPENDENT CLAIM is also included for a diagnostic tool for determining the resistance of a patient to at least one HIV therapy comprising the cut-off fold resistance value for the therapy as determined by the above method.

USE - (M1) is useful for predicting resistance of a disease caused at least in part by infection with a pathogen such as bacteria, virus (e.g. human **immunodeficiency** syndrome, hepatitis C or hepatitis B), prions, fungae, algae or protozoa, or caused by replication of malignant cells, to at least one therapy. The therapy is antiviral therapy comprising protease inhibitor therapy or reverse-transcriptase inhibitor therapy (non-nucleoside reverse-transcriptase inhibitor therapy). The therapy includes treatment with a AZT, ddI, ddC, d4T, abacavir, nevirapine, delavirdine, efavirenz, indinavir, ritonavir, nelfinavir, saquinavir, amprenavir, **lopinavir** or tenofovir. The therapy comprises an envelope inhibitor, fusion and integrase inhibitor treatment (claimed). The method is also useful for determining the resistance of the virus isolate to various antiviral drugs, and to improve the accuracy of predicting disease's clinical response to a particular therapy or combination of therapies.

ADVANTAGE - The newly defined cut-off values, termed biological cut-off values, are a more accurate reflection of natural variation in the population and may prove to be more predictive of clinical response than virological cut-off values.

Dwg.0/7

L19 ANSWER 92 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-147757 [19] WPIX
DOC. NO. CPI: C2002-045834
TITLE: Use of at least one synthetic, non-hormonal 21-aminosteroid for the treatment of a viral infection

e.g. hepatitis viral infection.
DERWENT CLASS: B01 B05
INVENTOR(S): PRENDERGAST, P T
PATENT ASSIGNEE(S): (KOTZ-I) KOTZE G S; (PREN-I) PRENDERGAST P T
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001097749	A2	20011227	(200219)*	EN	47<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001074383	A	20020102	(200230)		<--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001097749	A2	WO 2001-IB1101	20010622
AU 2001074383	A	AU 2001-74383	20010622

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001074383	A	Based on	WO 2001097749

PRIORITY APPLN. INFO: IE 2001-275 20010321; IE 2000-511 20000623

AB WO 200197749 A UPAB: 20020321
NOVELTY - A substance or composition comprises at least one synthetic, non-hormonal 21-aminosteroid(I).

ACTIVITY - Virucide; Hepatotropic; Antiinflammatory; Anti-HIV.

Cells were pre-grown in 12-well tissue culture plates using Eagle's minimum essential medium (EMEM supplemented with 10% heat inactivated fetal bovine serum (FBS), L-glutamine and gentamicin). Antiviral assays were designed to test six concentrations of Tirilazad mesylate(test)/Ribavirin(control) in triplicate against the challenge virus. The virus was diluted in EMEM without serum and an inoculum of 0.5 ml per well was adsorbed for 4 hours. Cell control cultures were sham inoculated with EMEM (0.5 ml) without serum. After virus adsorption, the inoculum was removed and 1.0 ml of the appropriate drug dilution in EMEM + 10% heat inactivated FBS + 0.1% DMSO was added. Cells and virus controls were refed with medium alone. The plates were incubated at 37 deg. C in a humified atmosphere containing 5% CO2 until plaques were formed. The cultures were fixed with 10% formalin and stained with methylene blue. Plaques were counted. Plaque reduction was determined by comparing the mean plaque count of drug treated cultures with the mean plaque number in the untreated virus infected control cultures and expressed in percent. The comparison of test/control compounds on anti-viral effect (MDBK/BVDV EC50(micro g/ml)) cytotoxicity (MDBK TC50(micro g/ml)) and therapeutic index was 7.5/1.7;84.1/7.0 and 11.2/4.2. The result showed that the therapeutic index of the test was superior to the control in the BVDV model of hepatitis C virus.

MECHANISM OF ACTION - 21-Aminosteroid metabolism inhibitor.

USE - For the treatment of a viral infection e.g. hepatitis viral infection caused by hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, BVDV, hog cholera virus or sheep border disease virus infection; for the treatment of viral infection caused by a retrovirus, by HIV or AIDS virus, Epstein Barr virus, Herpes virus, Cytomegalovirus or an animal virus, by a lipid envelope virus; for treating AIDS related syndromes including cachexia and/or wasting syndrome; to prevent a future viral infection and/or to combat the effects of a present or future virus infection; to regulate a dysregulated immune system(all claimed).

ADVANTAGE - The substance or composition potentiates or intensifies the effectiveness of the immune system. The substance or composition has enhanced solubility and maximal bioavailability.

Dwg.0/5

L19 ANSWER 93 OF 93 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-597217 [67] WPIX
CROSS REFERENCE: 2002-121422 [16]; 2003-875322 [81]; 2005-417059 [42]
DOC. NO. CPI: C2001-176746
TITLE: New crystalline forms of **lopinavir**, useful for producing pure forms of **lopinavir**, useful in the treatment of HIV (human **immunodeficiency** virus).
DERWENT CLASS: B03
INVENTOR(S): CHEMBURKAR, S; DICKMAN, D A; FORT, J J; HENRY, R F; LECHUGA-BALLESTEROS, D; NIU, Y; PORTER, W; HENERY, R F; LECHUGA, B D
PATENT ASSIGNEE(S): (ABBO) ABBOTT LAB
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001074787	A2	20011011	(200167)*	EN	88<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2001050920	A	20011015	(200209)		<--
NO 2002004679	A	20020930	(200304)		<--
EP 1268442	A2	20030102	(200310)	EN	<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
CZ 2002003529	A3	20030212	(200317)		<--
SK 2002001483	A3	20030204	(200318)		<--
KR 2003011807	A	20030211	(200339)		<--
CN 1422259	A	20030604	(200356)		<--
US 6608198	B2	20030819	(200356)		<--
JP 2003529592	W	20031007	(200370)		85<--
ZA 2002006962	A	20031126	(200402)		92<--
HU 2003002675	A2	20031229	(200413)		<--
MX 2002009559	A1	20030501	(200415)		<--
NZ 521183	A	20040326	(200425)		
BR 2001009433	A	20040810	(200455)		
IN 2002001243	P3	20050304	(200547)	EN	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001074787	A2	WO 2001-US9112	20010321
AU 2001050920	A	AU 2001-50920	20010321
NO 2002004679	A	WO 2001-US9112	20010321
		NO 2002-4679	20020930
EP 1268442	A2	EP 2001-924250	20010321
		WO 2001-US9112	20010321
CZ 2002003529	A3	WO 2001-US9112	20010321
		CZ 2002-3529	20010321
SK 2002001483	A3	WO 2001-US9112	20010321
		SK 2002-1483	20010321
KR 2003011807	A	KR 2002-712849	20020927
CN 1422259	A	CN 2001-807688	20010321
US 6608198	B2 Provisional	US 2000-193573P	20000330
		US 2001-793536	20010227
JP 2003529592	W	JP 2001-572482	20010321
		WO 2001-US9112	20010321
ZA 2002006962	A	ZA 2002-6962	20020829
HU 2003002675	A2	WO 2001-US9112	20010321
		HU 2003-2675	20010321
MX 2002009559	A1	WO 2001-US9112	20010321
		MX 2002-9559	20020927
NZ 521183	A	NZ 2001-521183	20010321
		WO 2001-US9112	20010321
BR 2001009433	A	BR 2001-9433	20010321
		WO 2001-US9112	20010321
IN 2002001243	P3	WO 2001-US9112	20010321
		IN 2002-MN1243	20020911

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001050920	A Based on	WO 2001074787
EP 1268442	A2 Based on	WO 2001074787
CZ 2002003529	A3 Based on	WO 2001074787
SK 2002001483	A3 Based on	WO 2001074787
JP 2003529592	W Based on	WO 2001074787
HU 2003002675	A2 Based on	WO 2001074787
MX 2002009559	A1 Based on	WO 2001074787
NZ 521183	A Based on	WO 2001074787
BR 2001009433	A Based on	WO 2001074787

PRIORITY APPLN. INFO: US 2001-793536 20010227; US 2000-538257 20000330; US 2000-193573P 20000330

AB WO 200174787 A UPAB: 20050725
NOVELTY - A crystalline hydrated form of **lopinavir** ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-onyl)-3-methylbutanoyl)amino-1,6-diphenylhexane), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a substantially pure hydrated form of **lopinavir**;
(2) a solvated crystalline form of **lopinavir** with a peak in the solid state infrared spectrum at a position within the range 1652-1666 cm-1 and a peak in the solid state infrared spectrum at a position within the range 1606-1615 cm-1;

(3) a solvated crystalline form of **lopinavir** with peak in the solid state infrared spectrum at a position 1661-1673 cm-1, and a peak in the solid state at 1645-1653 cm-1 and a peak in the solid state infrared spectrum at 1619-1629 cm-1;

(4) a pure solvated crystalline form of **lopinavir** with a peak in the solid state form at 1661-1673 cm-1 a peak in the solid state form in the range 1645-1653 cm-1 and a peak in the solid state infrared spectrum at a position 1619-1629 cm-1;

(5) a crystalline form of **lopinavir** with a peak in the solid state infrared spectrum at 1655-1662 cm-1;

(6) a crystalline form of **lopinavir** with a peak in the solid state form at 1655-1662 cm-1 and a peak at 1663-1647 cm-1;

(7) a substantially pure crystalline form of **lopinavir** with a peak in the solid state infrared spectrum at 1655-1662 cm-1;

(8) a substantially pure crystalline form of **lopinavir** with a peak in the solid state form at 1655-1662 cm-1 and a peak at 1663-1647 cm-1;

(9) a solvated crystalline form of **lopinavir** with a peak in the solid state infrared spectrum at 1655-1662 cm-1;

(10) a solvated crystalline form of **lopinavir** with a peak in the solid state form at 1655-1662 cm-1 and a peak at 1663-1647 cm-1;

(11) a substantially pure solvated crystalline form of **lopinavir** with a peak in the solid state infrared spectrum at 1655-1662 cm-1;

(12) a substantially pure solvated crystalline form of **lopinavir** with a peak in the solid state form at 1655-1662 cm-1 and a peak at 1663-1647 cm-1;

(13) a non-solvated crystalline form of **lopinavir**; and

(14) a substantially pure non-solvated crystalline form of **lopinavir**.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - HIV (human **immunodeficiency** virus) protease inhibitors; HIV infection inhibitors.

USE - The new crystalline forms of **lopinavir** can be used to purify or isolate **lopinavir** or can be used in the preparation of pharmaceutical compositions for the administration of **lopinavir**, a drug used in the treatment of HIV (human **immunodeficiency** virus).

ADVANTAGE - The new crystalline forms of **lopinavir** are useful for the preparation of purer forms of **lopinavir**.

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